



Trip Report for

**232nd American Chemical Society Meeting, San Francisco, CA
September 10 – September 14, 2006**

**Matthew Isherwood, Ph.D; Alexander Usyatinsky, Ph.D.;
Nadezhda Astakhova, Ph.D.**

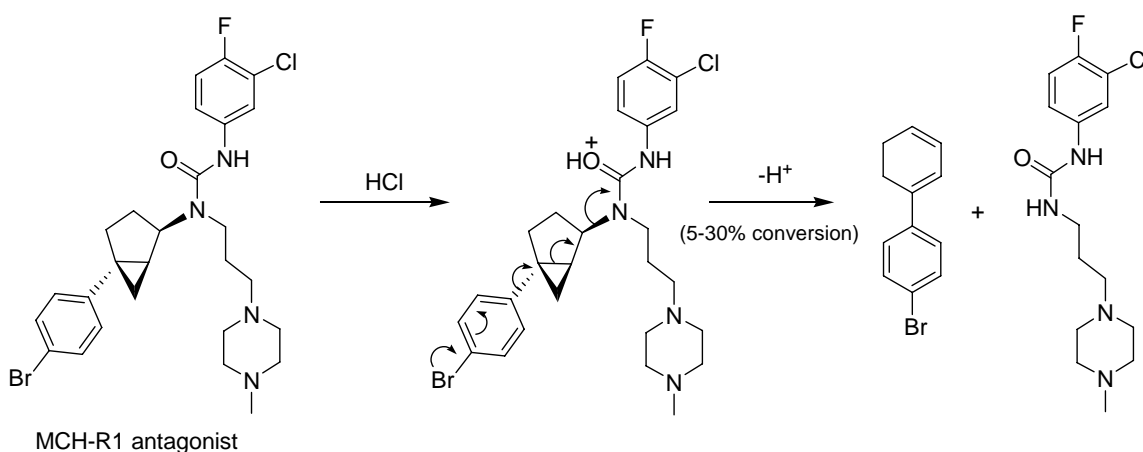
Abstract: *The 232nd ACS meeting was a platform for a large number of lectures and poster sessions covering varied topics of chemistry presented from members of industry and academia. This report highlights various presentations, from the meeting, of interest to medicinal and synthetic organic chemists.*

“Regioselective Bicyclo[3.1.0]hexyl Urea MCH-R1 Antagonists: Addressing the Fragmentation Issues of Bicyclohexyl Ureas,”

John W. Clayder; Kathleen Cox; Brian Hawes; Mark D. McBriar; Kim O'Neill; Daniel J. Weston; and Ruo Xu (Schering-Plough Research Institute).

Researchers from Schering-Plough presented some of their ongoing work in the development of Melanin-concentrating hormone receptor-1 (MCH-R1) antagonists for potential treatment of obesity. Previous work had identified a series of urea-based compounds which demonstrated oral efficacy in reducing food intake and weight gain in diet-induced obese (DIO) rodent models. These compounds incorporated a novel bicyclic[3.1.0]hexyl motif which had been identified as a viable isostere replacement for a potentially mutagenic biaryl aniline¹. However, during preparation of some analogs in the new series an instability problem was noticed that led to the fragmentation of the molecule. This presumably resulted from an acid catalyzed opening of the cyclopropyl ring moiety (Scheme 1). The degree of this fragmentation was found to be dependant on the substitution of the neighboring aryl ring. Fragmentation was most prevalent with electron donating *para*- aryl substituents which presumably assist in the formation of a resonance stabilized action intermediate. However, some substitutions such as 4-CN, 4-OCF₃, 4-F showed minimal (<1%) fragmentation. Additionally, pharmacokinetic rodent studies showed no evidence of metabolites formed via this route.

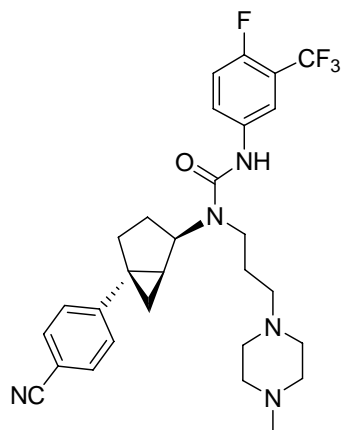
Scheme 1



Given these results it was still thought important to investigate further structural modifications which hopefully could preclude this fragmentation altogether. One approach to stabilize the bicyclo[3.1.0]hexyl core was to move the cyclopropyl group thus creating a regioisomeric series (Scheme 2). This created a “cross-conjugated” series of compounds wherein the cyclopropyl group is no longer adjacent to pendant urea. Synthesis of a series of analogs revealed a similar SAR to that established in the original series whereby in particular the 1,3-*trans* relationship of aryl-group to urea proved more active than the 1,3-*cis* case. Overall comparison of K_i values showed that the new series had generally 2-3 fold lower affinities for MCH-R-1 than the original series. More positively, many compounds showed improved pharmacokinetic properties such AUC

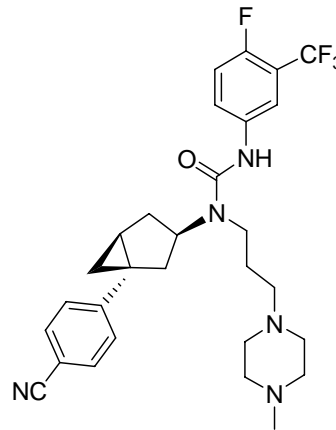
over the initial “conjugated series” and importantly these compounds did not display the inherent instability under acidic conditions (1 N HCl), no fragmentation was detected regardless of the nature of the aryl substituent.

Scheme 2



"Conjugated Series"

MCH R-1 $K_i = 2.7$ nm
Rapid Rat AUC = 642 ng·h/mL

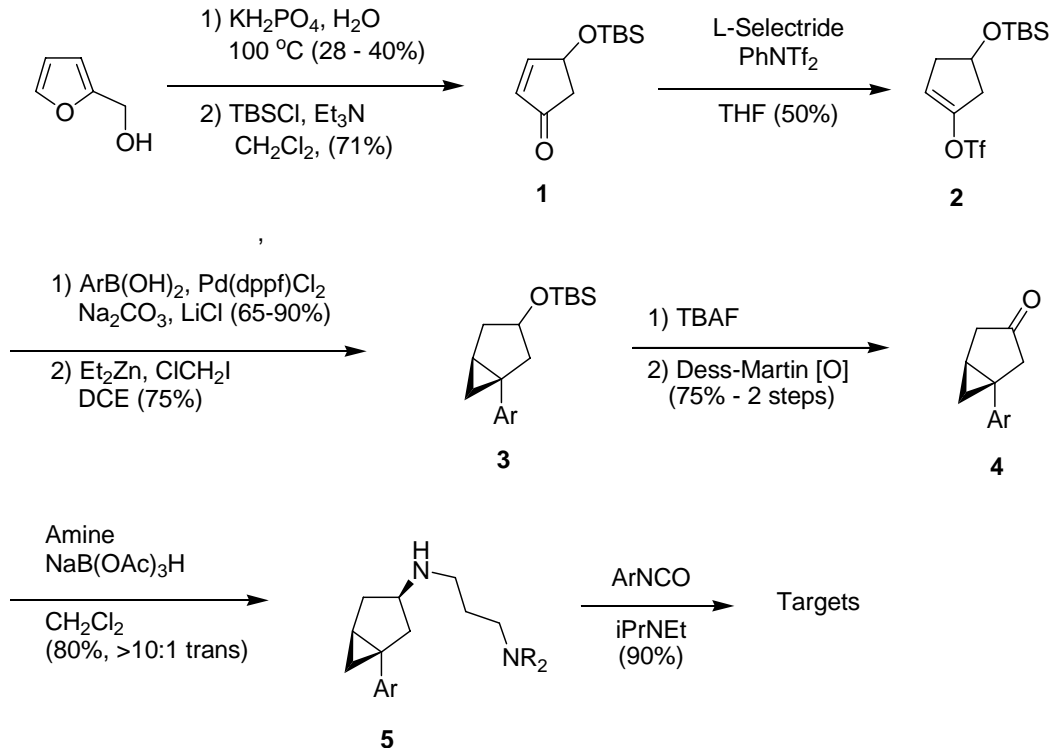


"Cross-Conjugated Series"

MCH R-1 $K_i = 8$ nm
Rapid Rat AUC = 802 ng·h/mL

The synthesis of the new regio-isomeric series was accomplished by using vinyl triflate **2** (Scheme 3) as a key intermediate for various Suzuki couplings. The vinyl triflate was synthesized in three steps from furfuryl alcohol. Acid-catalyzed rearrangement followed by TBS-protection afforded cyclopentenone **1**. Conjugate reduction with L-selectride and trapping of the resulting enolate afforded **2** in moderate yield. The required aryl groups were then installed in good yields with Suzuki couplings and the resulting alkenes cyclopropanated with Denmark's modified Simmons-Smith conditions. Desilylation and Dess-Martin oxidation afforded ketones of structure **4**. The pendant amine side chains were then incorporated by a standard reductive amination conditions giving the more active *trans*-isomers with a high degree of diastereoselectivity. Finally, addition of an aryl isocyanate afforded the target ureas.

Scheme 3



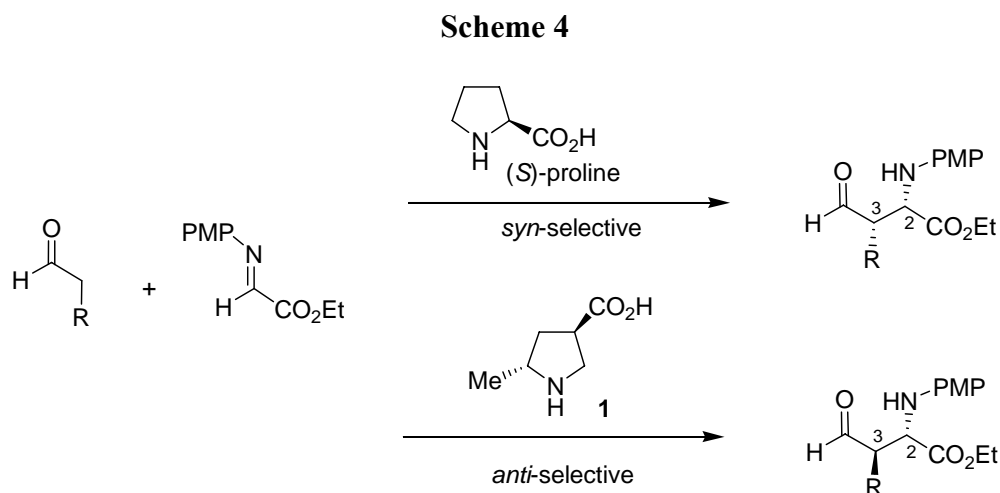
Reference:

- 1) McBriar, M. D.; Guzik, H.; Shapiro, S.; Paruchova, J.; Xu, R.; Palani, A.; Clader, J. W.; Cox, K.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T. J.; O'Neill, K.; Spar, B. D.; Weig, B.; Weston, D. J.; Farley, C.; Cook, J. J. *Med. Chem.* **2006**, *49*, 2294-2310.

“Discovery and Design in Organocatalysis,”

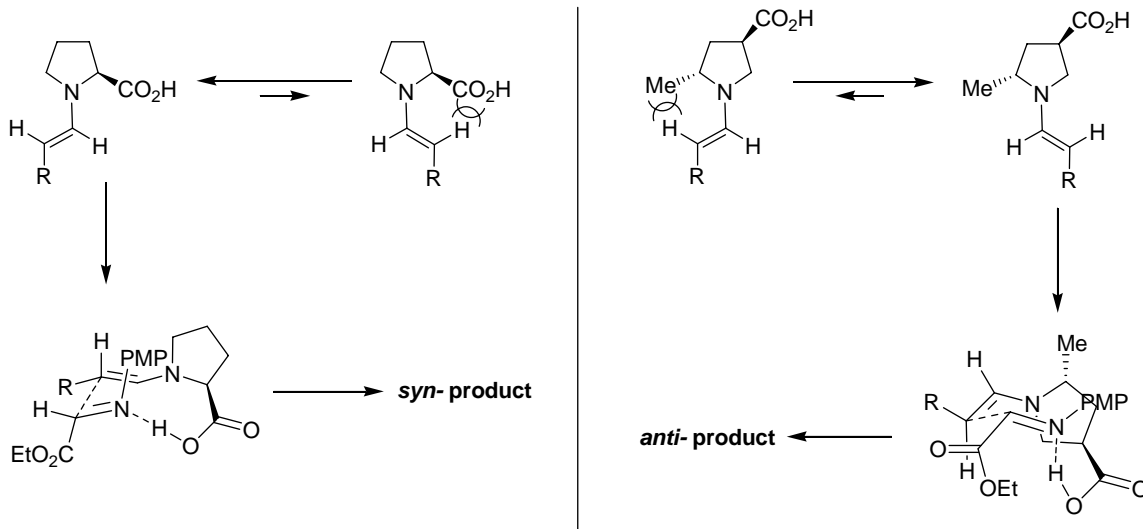
K. Albertshofer; C. F. Barbas III; N. S. Chowdari; N. Mase; D. S. Mitsomori; D. Ramachary; S. S. V. Ramasastry; D. Steiner; J. T. Suri; F. Tanaka; N. Utsumi; H. Zhang. (The Scripps Research Institute).

A representative from the Barbas group presented recent developments in their studies toward catalytic asymmetric *anti*-Mannich-type reactions using solely organic catalysts. Previous work in the group had shown that the reaction of unmodified aldehydes with *N*-*p*-methoxyphenyl (PMP) protected imines could be catalyzed by (*S*)-proline to give (*2S,3S*)-*syn*-amino aldehydes with a high degree of enantioselectivity (Scheme 4). Traditionally the development of methodologies for corresponding *anti*-selective Mannich-type reactions have been more challenging and illusive. To this end the group set about designing a new catalyst based on the examination of key factors that control the (*S*)-proline catalyzed reactions. This work culminated in the discovery of pyrrolidine derivative **1** as an efficient asymmetric *anti*-selective catalyst¹.



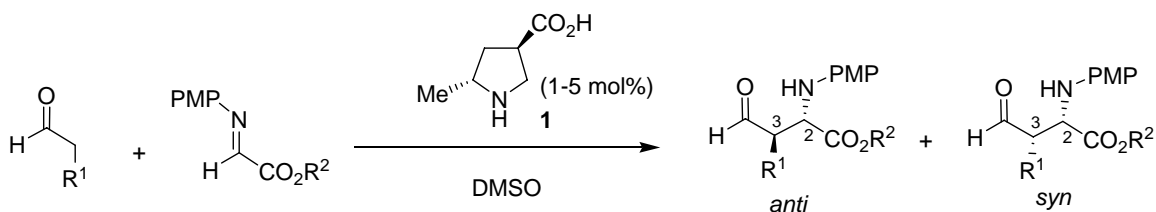
It was noted that in the (*S*)-proline catalyzed reactions, the *s-trans* confirmation of the (*E*)-enamine reacts in the C-C bond-forming transition state. Also, the carboxylic acid group was recognized as a key element in controlling facial selectivity and enabled proton transfer to the imine (Scheme 5). The new catalyst **1** incorporated an additional steric influence in the form of a methyl group at the 5-position of the pyrrolidine whilst the carboxylic acid group was simultaneously moved to the 3-position. It was thought that these changes would facilitate an inversion of the regiochemistry of the intermediate enamine. This effect coupled with a continued facial directing influence of the carboxylic acid group suggested that selectivity for *anti*-Mannich products might be possible. Computational studies using HF/6-31G* level of theory also gave support for these ideas. Of additional note, the *trans*-relationship of the C5-methyl and C3-CO₂H was also important since a *cis*-relationship of these groups would give rise to steric interactions with the imine in the transition state.

Scheme 5



The new catalyst proved to be effective in the reactions of various unmodified aldehydes giving predominantly *anti*-products with high levels of enantioselectivity (Scheme 6). Additionally, it was noted that the reaction rates were 2-3 fold faster than the corresponding proline catalyzed *syn*-selective reactions, thus allowing fairly low loadings (1-5 mol%) of **1** to be employed.

Scheme 6



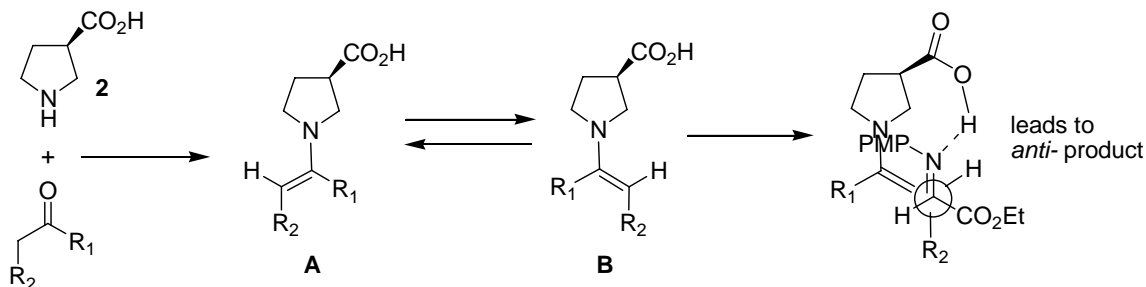
R ¹	R ²	time (h)	yield (%)	dr <i>anti:syn</i>	ee (%)
Me	Et	1	70	94:6	>99
<i>i</i> -Pr	Et	3	85	98:2	99
<i>n</i> -Bu	Et	0.5	54	97:3	99
<i>n</i> -Pent	Et	3	80	97:3	>99
CH ₂ CH=CH ₂	Et	3	72	96:4	>97
<i>i</i> -Pr	<i>i</i> -Pr	1	92	97:3	98
<i>n</i> -Pent	<i>i</i> -Pr	1	85	96:4	>99

Next efforts were directed toward the investigation of *anti*-Mannich-type reactions of ketones². Applying catalyst **1** under the same conditions which had been successful in the previous case with aldehydes however, gave disappointing results. The reaction

between 3-pentanone and *N*-PMP- α -imino ethyl glyoxylate (Scheme 7) was very slow giving <10% yield of product after 3 days. Noteworthy, is that proline has been shown to effectively catalyze the *syn*-Mannich-type reactions of ketones. Given this it was postulated that the reason for the slow reaction rate was relatively slow formation of enamine intermediate caused by steric interaction with the methyl group of the catalyst. From some of the previous work with aldehydes it was reasoned that a simplified, less hindered catalyst lacking the methyl might still display selectivity for *anti*-Mannich products since the 3-carboxylic acid alone seemed to have a role in stereoselection.

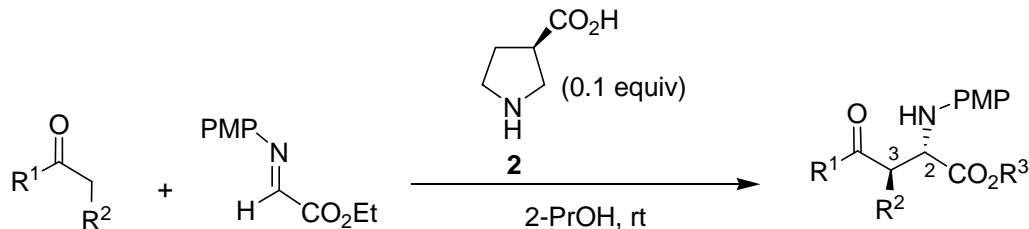
In the case of the simplified catalyst **2** (Scheme 7), it seems reasonable that the enamine intermediates **A** and **B** would have similar free energies and therefore exist in similar concentrations.

Scheme 7



However, it was reasoned that this distribution of enamine conformations was less important due to the organizing effect of the carboxylic acid of the catalyst on the transition state of the reaction. Conformation **B** apparently can form a transition state which involves proton transfer from the carboxylic acid to the imine substrate whereas in conformation **A** the acid proton would appear to be too distant for proton transfer to occur readily. In experiment this rational proved successful and catalyst **2** was shown to induce much higher reaction rates than **1** and more importantly produced *anti*-Mannich products with high levels of enantioselectivity. Further optimization identified 2-PrOH as the most favorable solvent for reaction rate, yield and *anti*-selectivity. Representative results are shown in Scheme 8.

Scheme 8



R ¹	R ²	time (h)	yield (%)	dr <i>anti:syn</i>	ee (%)
Et	Me	20	91	97:3	97
<i>n</i> -Pr	Et	96	76	>99:1	82
Me	Me	5	85	~10:1	90
Me	Et	10	81	~10:1	92
Me	CH ₂ CH=CH ₂	14	85	>95:5	91
Me	(CH ₂) ₃ Cl	14	68	>95:5	84

References:

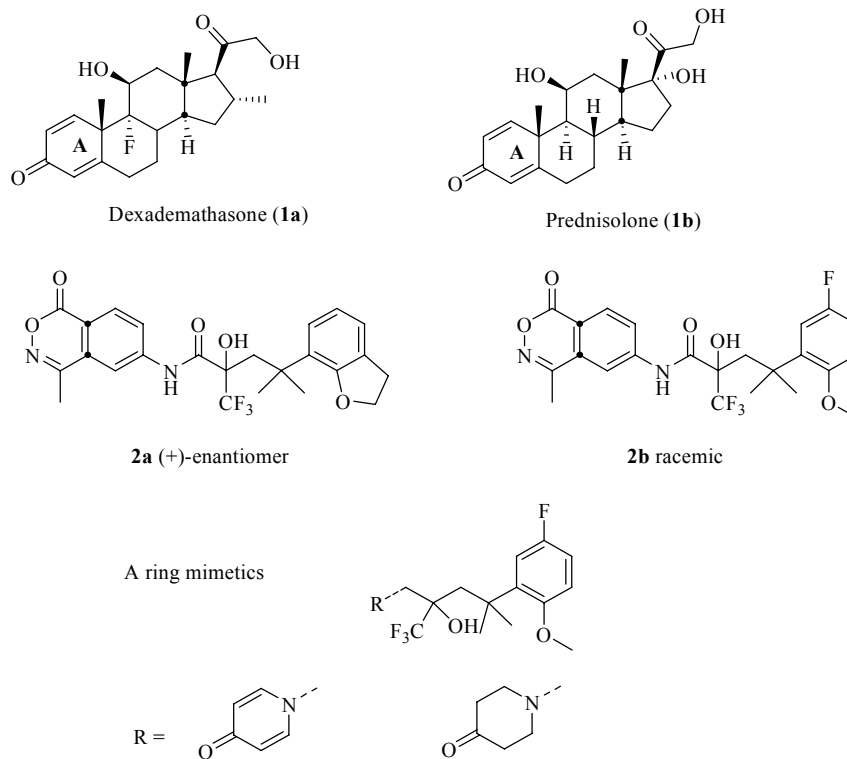
- 1) Mitsumori, S.; Zhang, H.; Ha-Yeon Cheong, P.; Houk, K. N.; Tanaka, F.; Barbas III, C. F. *J. Amer. Chem. Soc.* **2006**, *128*, 1040-1041.
- 2) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas III, C. F. *J. Amer. Chem. Soc.* **2006**, *128*, 9630-9631.

“Quinol-4-ones as Dissociated Non-Steroidal Glucocorticoid A-Ring Mimetics,”

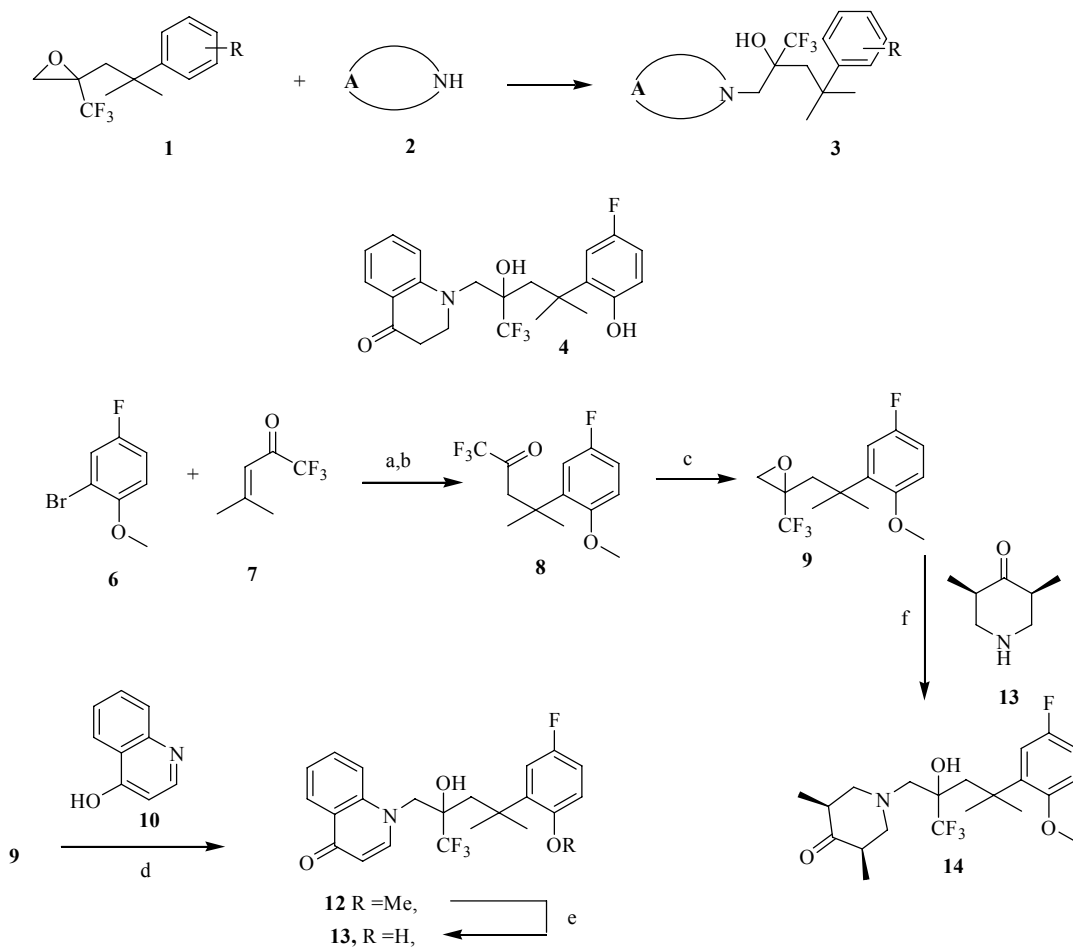
Younes Bekkali; Joerg Bentzien; Alison Capolino; Abdelhakim Hammach; Tom Kirrane; Daniel Kuzmich; Thomas Lee; Gerald H. Nabozny; Richard Nelson; John Proudfoot; Mark Ralph; John Regan; Donald Souza; Dianne Thome; David Thomson; Renee M. Zindell (Department of Medicinal Chemistry and Department of Pharmacology, Boehringer Ingelheim Pharmaceuticals, Inc.), 900 Ridgebury Road, Ridgefield, CT 06877.

Glucocorticoid agonists such as dexamethasone and prednisolone are effective in treatment of inflammatory diseases such as asthma and rheumatoid arthritis. However, these drugs have severe side effects and show cross-reactivity with other steroid hormone receptors such as progesterone (PR) and mineralocorticoids (MR). The goal of the reported work was to develop A ring mimetics that will take advantage of hydrogen bonding interaction with Arg611-Gln570 of the hormone receptor while retaining anti-inflammatory properties. Examples of A-ring mimetics with hydrogen bond accepting pharmacophores include phenylpyrazoles (GR), benzonitrile (aromatase), pyrrolidines (PR), benzoxazinone (**2a** and **2b**, Figure 1). The ideal lead should exhibit good affinity toward glucocorticoid receptor (GR), low off-target activity (binding with PR and MR) and high dissociated profile (greater transrepression, than transactivation activity). The transrepression potential is measured in human foreskin fibroblast (HFF) cells. Inhibition

of IL-1 stimulated of IL-6 production, and percent efficacy is compared with that of dexamethasone. In an effort to establish transactivation activity, compounds are counterscreened for induction aromatase (Aromat) in HFF cells. Comparisons with dexamethasone establish basis for identifying compounds with dissociated profile.

Figure 1

It was predicted, that epoxide ring opening of substrate **1** (Scheme 1) with nucleophiles **2** will provide products with general structures **3** and **4**.



Conditions: a: Mg powder, THF, heat; b: CuI (1.1 eq), -20°C , 90 min, r.t., overnight; c: trimethylsulfoxonium iodide, NaH, DMSO; d: **10** (0.9 eq.), NaOEt, EtOH, heat; e: BBr_3 (10 eq), CH_2Cl_2 , r.t., overnight; f: **13** (2 eq), K_2CO_3 (5 eq), DMF, 100°C , 1.5 h..

The SAR for A-ring mimetics is presented in Table 1.

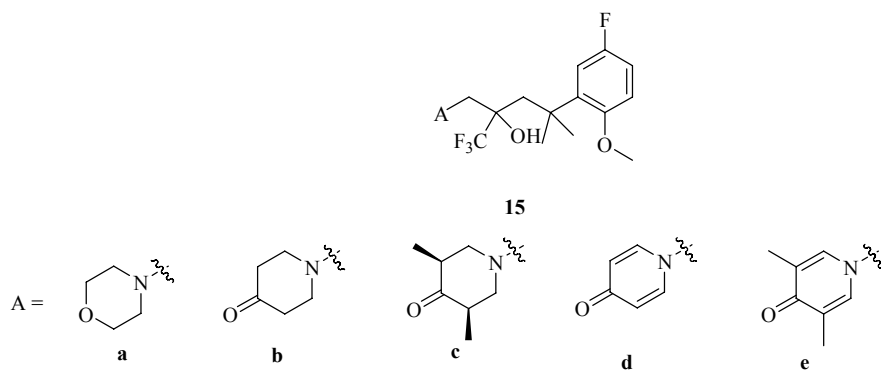
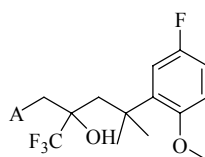


Table 1
Biological and Pharmacological data for A-ring mimetics, containing a carbonyl moiety.

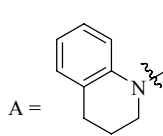
	1a	2a	2b	15a	15b	15c	15d	15e
GR IC ₅₀ (nM)	3	3	8	>2000	1400	10	>2000	12
PR IC ₅₀ (nM)	>2000	19	22	>2000	>2000	>2000	>2000	>2000
MR IC ₅₀ (nM)	33	38	130	>2000	>2000	430	>2000	1900
IL-6 IC ₅₀ (nM)	0.51	59	>2000	NA	NA	75	NA	53
Efficacy	100%	80%	19%	NA	NA	89%	NA	87%
Aromat EC ₅₀ (nM)	19	91	>2000	>2000	NA	246	NA	170
(% vs dex)	100%	56%	0%	12%	NA	93%	NA	77%

Conclusion: Carbonyl containing moieties bind to GR. Incorporation of methyl groups flanking the carbonyl enhance binding. Compounds exhibit a good activity in inhibition of IL-6 release from human foreskin fibroblast cells (HFF)

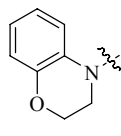
Table 1 (continued)



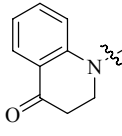
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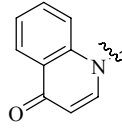
a



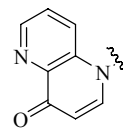
b



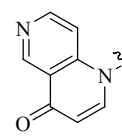
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d



e



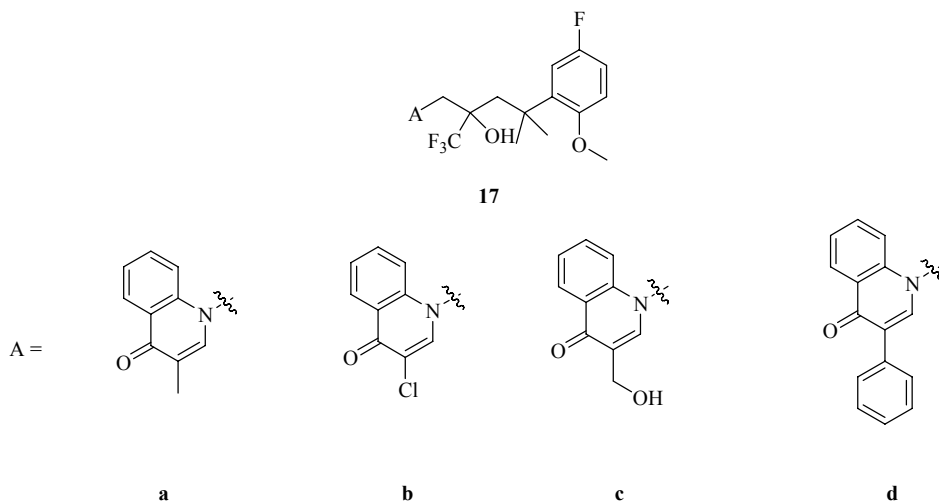
f

	16a	16b	16c	16d	16e	16f
GR IC ₅₀ (nM)	950	15	4	10	77	34
PR IC ₅₀ (nM)	>2000	640	90	470	>2000	>2000
MR IC ₅₀ (nM)	1600	310	130	120	1100	175
IL-6 IC ₅₀ (nM)	-	600	110	21	56	35
Efficacy	-	25%	72%	82%	78%	82%
Aromat EC ₅₀ (nM)	>2000	>2000	>2000	221	IP*	IP*
(% vs dex)	3%	11%	25%	67%	41%	39%

*curve is too shallow to accurately determine an EC₅₀

Conclusion: Hydrogen bonding acceptor is required for IL-6 activity. Increasing lipophilicity of A-ring with benzofused moieties improves agonist activity. GR/PR selectivity is compromised with addition of benzofused moieties. GR/MR selectivity remains unchanged. Novel A-ring mimetic is identified in quinol-4-one.

Table 1 (continued)



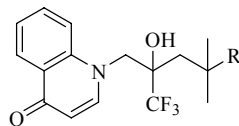
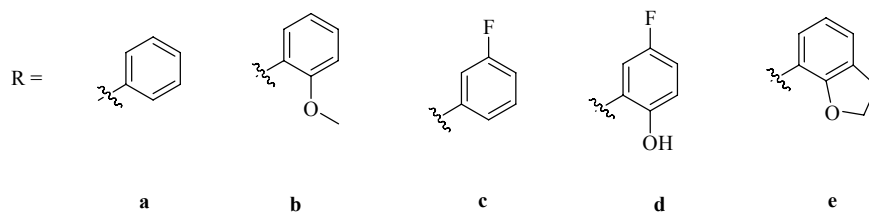
	16d	17a	17b	17c	17d
GR IC ₅₀ (nM)	10	6	6	92	>2000
PR IC ₅₀ (nM)	470	>2000	>2000	>2000	>2000
MR IC ₅₀ (nM)	120	125	125	1500	>2000
IL-6 IC ₅₀ (nM)	21	101	125	370	-
Efficacy	82%	86%	82%	59%	-
Aromat EC ₅₀ (nM)	221	IP*	IP*	IP*	IP*
(% vs dex)	67%	65%	55%	5%	-

*curve is too shallow to accurately determine an EC₅₀

Conclusion: 3-substitution of the quinol-4-one can lead to increased GR/PR selectivity but is dependant on size.

The next step of lead optimization was to study the effect of the right hand side modification. The results of this study are presented in Table 2.

Table 2
Effect of right hand side modification.

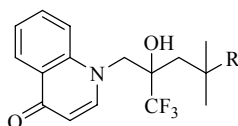
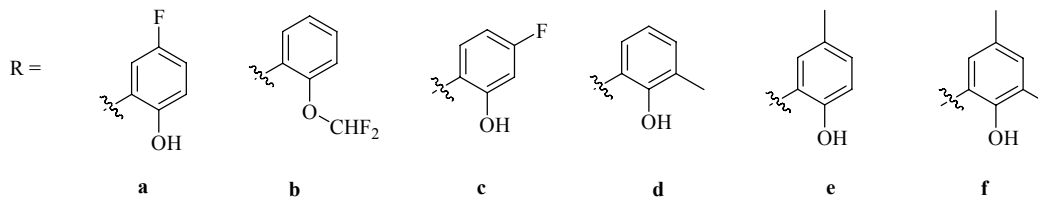
**18**

	18a	18b	18c	18d	18e
GR IC ₅₀ (nM)	4	6	29	10	4
PR IC ₅₀ (nM)	48	135	225	475	48
MR IC ₅₀ (nM)	98	110	605	145	98
IL-6 IC ₅₀ (nM)	11	16	>2000	27	11
Efficacy	86%	78%	-	81%	88%
Aromat. EC ₅₀ (nM)	37	36	>2000	221	IP*
(% vs dex)	83%	47%	-	67%	60%

*curve is too shallow to accurately determine an EC₅₀

Conclusion: Dissociation and nuclear receptor selectivity can be modulated by variation of the right-hand side of the molecule.

Table 2 (continued)

**19**

	19a	19b	19c	19d	19e	19f
GR IC ₅₀ (nM)	5	6	18	3	8	19
PR IC ₅₀ (nM)	960	605	340	1300	160	1850
MR IC ₅₀ (nM)	615	300	780	1300	140	625
IL-6 IC ₅₀ (nM)	6	31	3	150	6	220
Efficacy	92%	70%	88%	69%	93%	72%
Aromat EC ₅₀ (nM)	14	IP*	11	>2000	32	IP*
(% vs dex)	74%	29%	83%		79%	31%

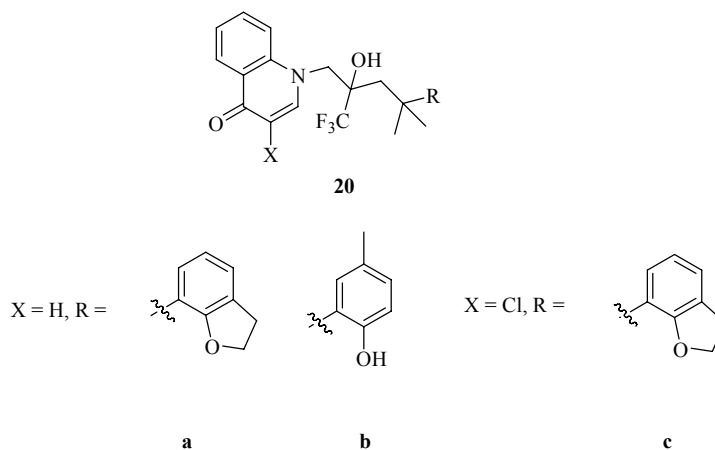
*curve is too shallow to accurately determine an EC₅₀

Conclusion: Right-hand side modification can build in dissociation as well as GR/PR and or GR/MR selectivity.

It was concluded, that distinction between transrepression activity and diminished transactivation could be achieved with proper choice of A-ring replacement and phenyl substations with this class of compounds.

Selected compounds were tested *in vivo* for their anti-inflammatory properties in LPS-stimulated mouse model for TNF- α production. Test compounds were administered orally in cremophor 60 minutes prior to LPS challenge. TNF- α levels were measured 60 minutes later. Each compound was tested in group containing 8 mice. The results are presented in Table 3.

Table 3
In vivo data: inhibition of TNF- α in mice.



	20a	20b	20c
IL-6 IC ₅₀ (nM)	11	6	30
Efficacy	86%	93%	84%
Aromat EC ₅₀ (nM)	IP*	32	170
(% vs dex)	60%	79%	65%
% Inhibition of TNF- α (10 mpk)	49	63	86

*curve is too shallow to accurately determine an EC₅₀

Conclusion: Dissociated agonists retain anti-inflammatory activity *in vivo*, therefore non-steroidal compounds with selective mechanism of action (transrepression over transactivation) could be used as anti-inflammatory agents without significant side effects.

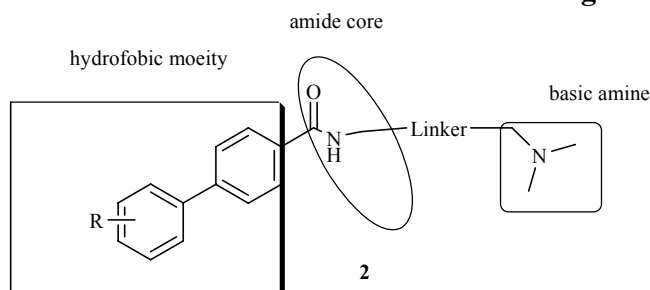
General conclusion: Novel A-ring mimetics were identified as nonsteroidal dissociated glucocorticoid agonist. The GR/PR selectivity for simple quinol-4-ones was compromised. However, selectivity could be built back in by modifications of both the right hand side as well as the A-ring. In addition, changes to the right-hand side led to potent dissociated compounds. Compounds such as these may lead to non-steroidal anti-inflammatory agents with reduced side effects.

“MCH receptor-1 antagonists for the treatment of obesity,”

Kamal A. Al-Barazanji; Kevin K. Barvian; Andrew J. Carpenter; Joel P. Cooper; Aaron S. Goetz; Gary M. Green; Yu C. Guo; Anthony L. Handlon; Donald L. Hertzog; Clifton E. Hyman; Gregory E. Peckham; Jason D. Speake; Francis X. Tavares; Hui-qiang Zhou (Medicinal Chemistry, GlaxoSmithKline), P.O. Box 13398, Research Triangle Park, NC 27709-3398.

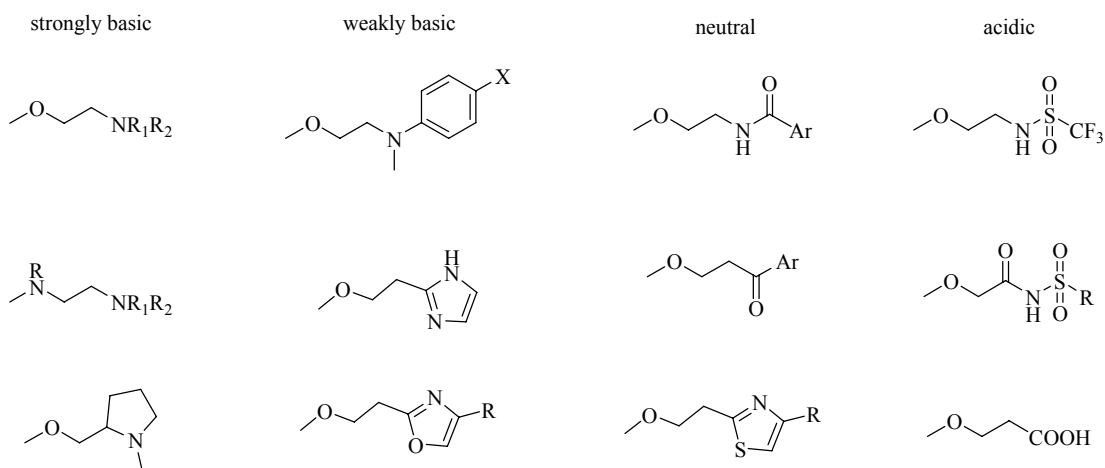
It was previously reported that compound GW803430X (Figure 1) is a potent MCHR-1 antagonist that causes significant weight loss in DIO mice. Many MCHR-1 antagonists share a common pharmacophore (**2**, Figure 1).

Figure 1
Common structural motif for MCHR-1 antagonists.



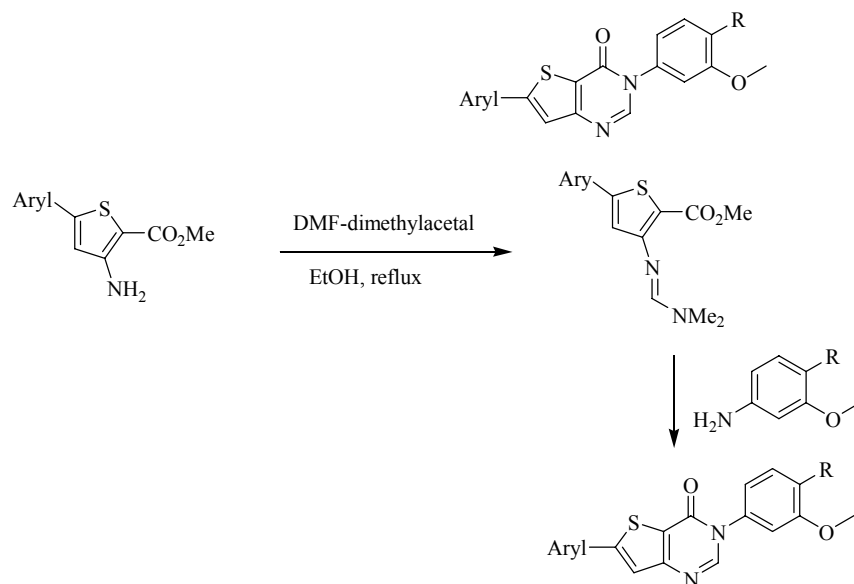
It was found; the highly potent basic RHS amines have significant off target activities. Therefore the authors set out to explore analogues of GW803430X that replaced the basic amine with hydrogen bond acceptors that are not basic. The possible right-hand substituents are presented below.

Figure 1
Right-hand substituents.

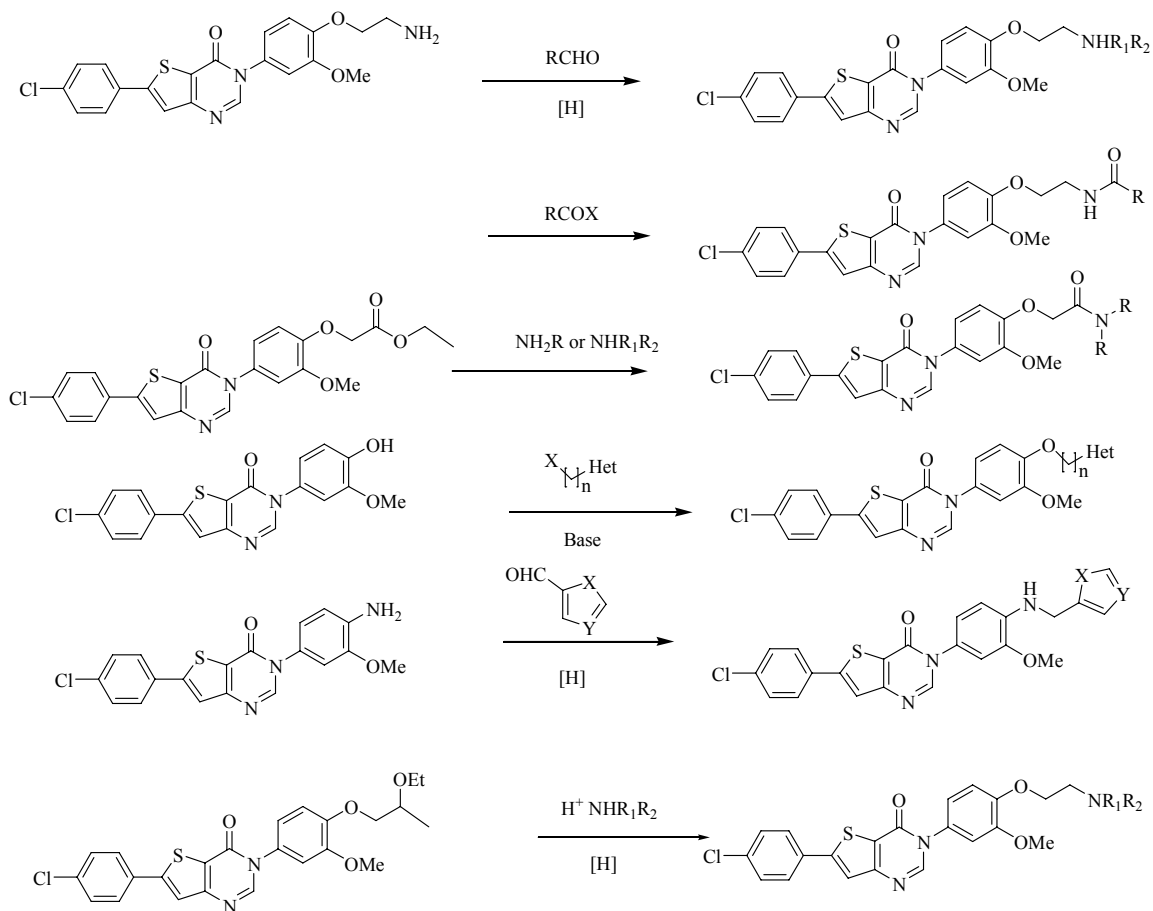


The synthesis of potential leads included the construction of a thinenylpyrimidine scaffold followed by elaboration of the right-hand side (Scheme 2).

Scheme 2 Synthesis of the Thienylpyrimidenone Scaffold

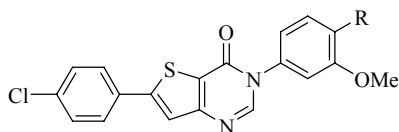


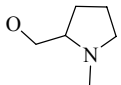
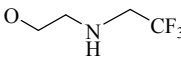
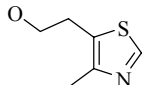
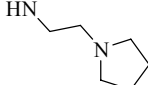
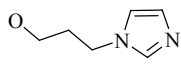
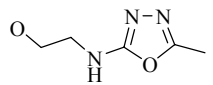
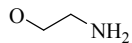
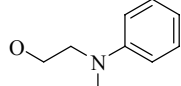
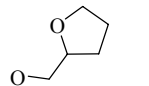
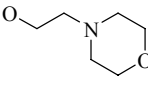
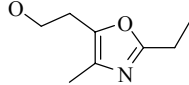
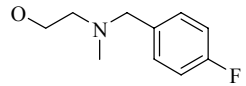
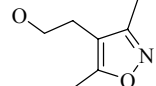
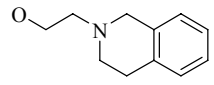
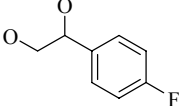
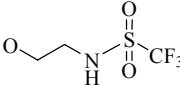
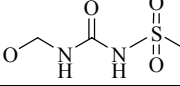
Scheme 2 (continued)
Elaboration of the right-hand side.



Inhibition of the MCHR-1 receptor was determined *in vitro* and the results obtained are presented in Table 1.

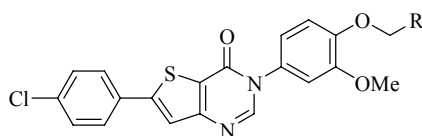
Table 1
***In vitro* inhibition of MCHR-1.**



R (strongly basic)	pIC ₅₀ *	R (weakly basic)	pIC ₅₀ *	R (neutral)	pIC ₅₀
	8.7		7.7		9.1
	8.8		8.5		8.2
	9.1		7.5		8.5
	8.9				8.4
	9.0				7.7
	8.5				8.3
R (acidic)	pIC ₅₀				
	7.5				
	7.5				

*[pIC₅₀ = -log(IC₅₀)]

Table 1 (continued)
***In vitro* inhibition of MCHR-1.**



R (heterocyclic)	pIC ₅₀ *	R (heterocyclic)	pIC ₅₀ *
	8.5		8.2
	8.1		8.0
	8.4		8.5
	8.5		8.4

*[pIC₅₀ = -log(IC₅₀)]

Table 1 (continued)
***In vitro* inhibition of MCHR-1 (pIC₅₀ = -log(IC₅₀)).**

R (nitroethylendiamines)	pIC ₅₀ *	R (cyanoguanidines)	pIC ₅₀ *
	7.9		8.3
	7.8		8.1
	8.2		8.7
	7.9		8.2

*[pIC₅₀ = -log(IC₅₀)]

Based on obtained data the authors concluded:

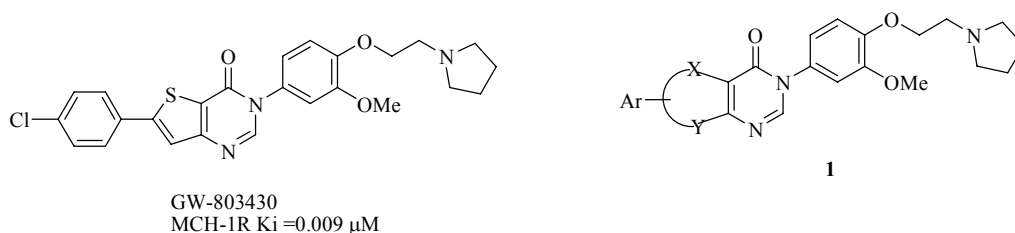
- A basic amine on the right hand side is not required for highly potent MCHR-1 inhibition.
- Non-basic heterocycles such as oxazoles and isoxazoles give better than 10nM IC₅₀.
- The side chained found in Ranitidine and Cimetidine (nitroethylenguanidine and cyanoguanidine, respectively) afford moderately potent MCH antagonist but have undesirable physical properties.
- Acidic side chains afford less potent MCHR-1 antagonists.

“Microwave assisted synthesis of thiazolo-, isothiazolo-, imidazolo-, and pyrimido-pyrimidinones as novel MCH1R antagonists,”

William Greenlee; Tao Guo; Rachael C. Hunter; Rui Zhang (*Pharmacopeia Drug Discovery, Inc*), P.O. Box 5350, Princeton, NJ 08543; (*Schering-Plough Research Institute*), 2015 Galloping Hill Road, Kenilworth, NJ 07033.

A known MCH-1R antagonists GW-803430 (Figure 1), is an orally efficacious compound discovered by GSK scientist. This compound has recently entered human clinical investigation for the treatment of obesity.

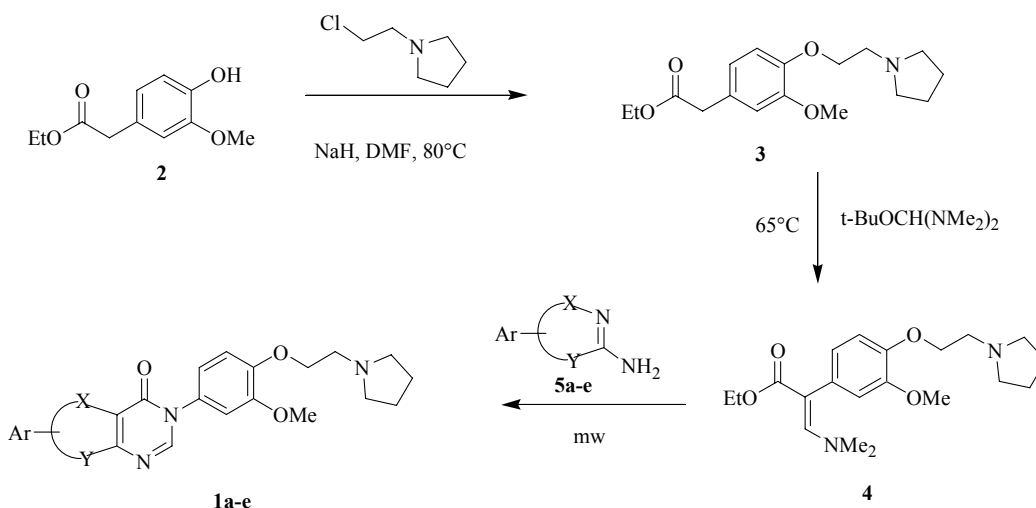
Figure 1



The goal of the current work was to design a series of fused biheterocyclic compounds (**1**, Figure 1) with thiazolo-isothiazolo and pyrimido-pyrimidinone cores as a replacement for the thienopyrimidine core in GW-803430.

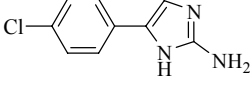
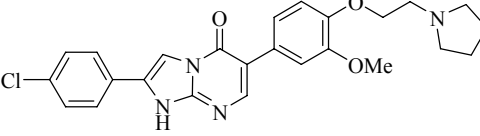
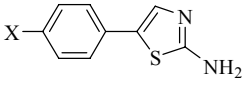
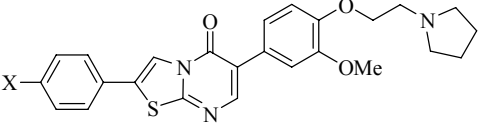
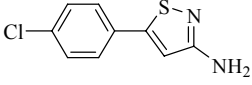
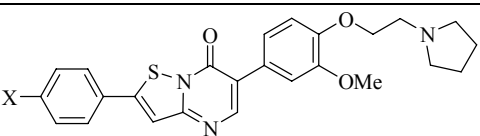
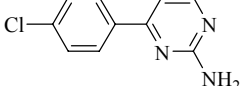
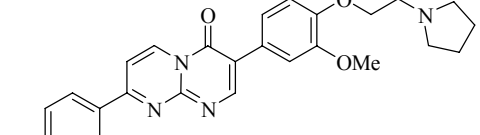
The synthesis of the target compounds is shown in the Scheme 1.

Scheme 1



Microwave assisted synthesis was used on the last step to increase the yield and reduce reaction time. The microwave conditions, yields and binding data are presented in Table 1.

Table 1

Substrate	Conditions	Product (yield %)	MCH-1R K _i (μM)
	220°C, 200 s AcOH	 1a (63%)	0.077
	200°C, 300 s AcOH	 1b X = H, (89) 1c X = Cl (65)	3.0 3.0
	200°C, 600 s AcOH	 1d, (44)	1.4
	200°C, 300 s AcOH	 1e, (49%)	1.8

It was concluded, that the use of microwave techniques improved yields and reduced the reaction time of the condensation of α -heteroarylamines **5** with 3-dimethylamino-2-arylpropenoate **4** (Scheme 1). The synthesized compounds **1a-e** displayed low to submicromolar activity in MCH-1R binding assay.

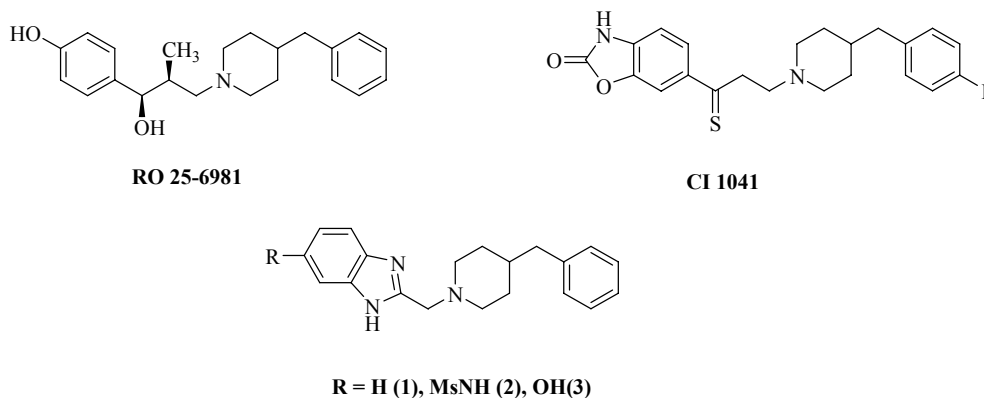
“Benzimidazol-2-carboximides as a novel, NR2B selective NMDA receptor antagonists,”

Béla Ágai; Ferenc Bertha; István Borzal; György Domány; József Fetter; Kornél Galgóczyi; Anikó Gerei; Sándor Kolokl; Ildikó Magdól; (Gedeon Richter Ltd.), Budapest 10. P.O. Box 27, H-1475 Hungary. Sándor Farkasl; Csilla Horváthl; György M. Keserűl (Budapest University of Technology and Economics), Budapest 11, P.O. Box 91, H-1521 Hungary.

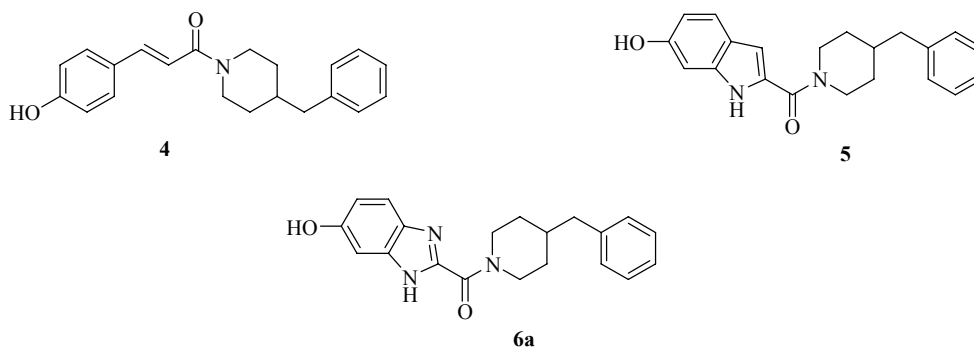
An important class of the NR2B subtype selective NMDA receptor antagonists can be characterized as an H-bond donor moiety containing an aromatic ring connected to the

nitrogen of 4-benzylpiperidine via a three-atom long spacer, such as in **Ro 25-6981**, **CI-1041** or **1-3** (Figure 1).

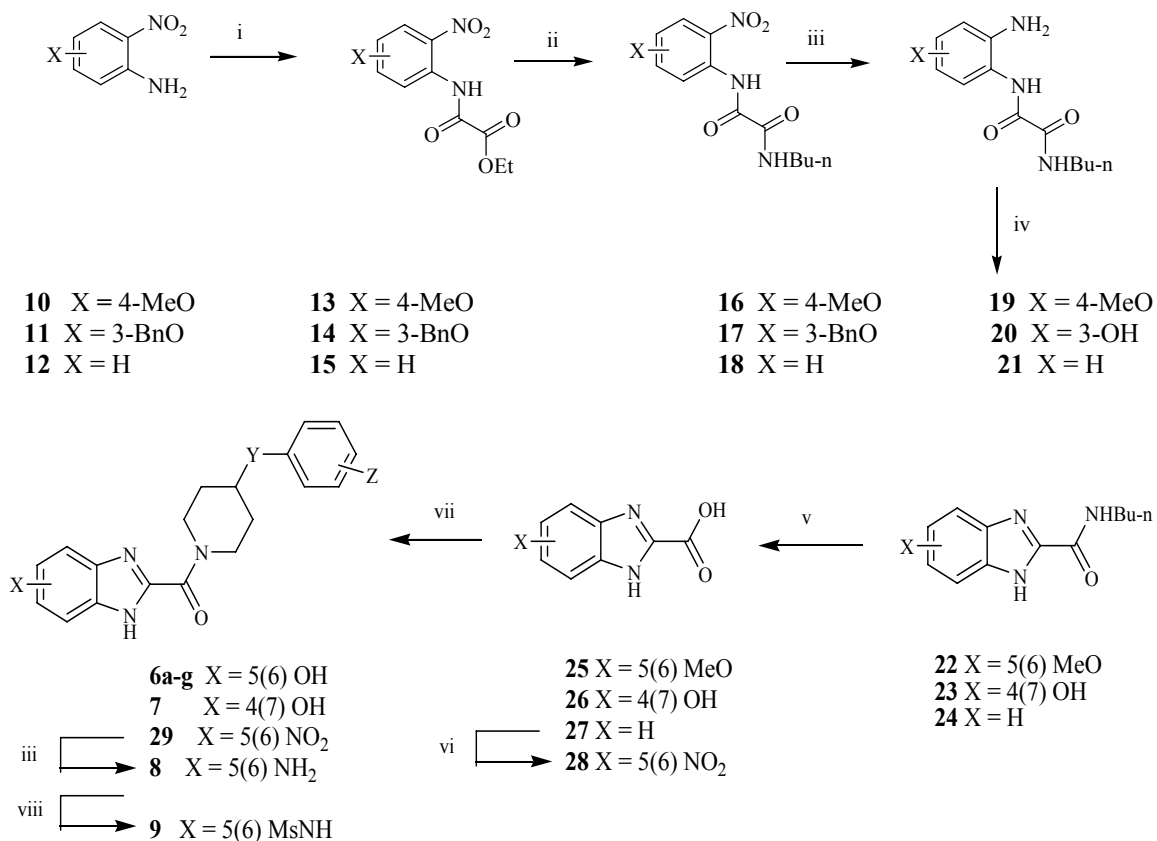
Figure 1
NMDA Receptor antagonists.



Cinnamide derivatives were the first NR2B subtype-selective NMDA receptor antagonists which did not contain basic nitrogen. Piperidine-based cinnamide **4** was selected from this family as the starting point for research. It was suggested that potency may be enhanced by increasing the rigidity of cinnamide moiety. Incorporation of an NH group between the α carbon atom and the benzene ring of the cinnamic acid part led to the 6-hydroxy-indole-2-carboxamide (**5**), with more than six-fold higher potency. Encouraged by this result, the authors decided to explore other heterobicyclic systems. Replacing the indole skeleton in compound **5** with the potentially bioequivalent benzimidazole ring-system resulted in a more active compound (**6a**). Therefore it was decided to prepare a series of benzimidazole-2-carboxamides.



The synthesis of possible leads was carried out in accordance with the following **Scheme 1**.



Reagents and conditions: (i) ClCOCOOEt, Et₃N, CH₂Cl₂, 0°C-rt; (ii) nBuNH₂, toluene, rt, 10 h; (iii) H₂, 10 % Pd/C, MeOH, rt; (iv) 240°C, 10 min; (v) 48 % HBr, reflux, 48 h; (vi) H₂SO₄-HNO₃; (vii) 4-substituted piperidine, HBTU, Et₃N, DMF; (viii) MesCl, pyridine, CH₂Cl₂, from 0°C to rt.

The results of biological testing for the series of substituted benzimidazole carboximides are presented in Table 1.

Table 1
Biological activity of the synthesized benzimidazole-2-carboxamides.

	X	Y	Z	NMDA-evoked D[Ca ²⁺] _i ^{a,b} IC ₅₀ (nM)	n	[³ H]Ro- 25,6981 binding ^a IC ₅₀ (nM)	n
6a	5(6)-OH	CH ₂	H	2.2 ± 0.4	4	4	2
6b	5(6)-OH	CH ₂	4-F	1.2 ± 0.3	5	4	2
6c	5(6)-OH	CH ₂	4-Me	8.7 ± 1.0	5	4.4 ± 1.2	3
6d	5(6)-OH	CH ₂	3-F	6.0 ± 1.1	3	5.2 ± 1.9	3
6e	5(6)-OH	CH ₂	3-Me	2.4 ± 0.5	4	5	2
6f	5(6)-OH	CH ₂	3-MeO	2.5 ± 0.6	3	3.2 ± 1.1	3
6g	5(6)-OH	CH ₂	2-Me	12.0 ± 2.8	10	8.4	2
6h	5(6)-OH	O	4-Me	1.1 ± 0.2	4	3	2
6i	5(6)-OH	O	4-Cl	1.7 ± 0.4	6	14	2
6j	5(6)-OH	O	4-F	2.9 ± 0.6	3	6	2
7	4(7)-OH	CH ₂	H	3.0 ± 0.4	4	10 ± 4	3
8	5(6)-NH ₂	CH ₂	H	40 ± 0.4	3	143	2
9	5(6)-MsNH	CH ₂	H	1.3 ± 0.2	4	3	2
2				8.6 ± 1.7	5	3.5 ± 1.1	3
4				131 ± 10	2	196 ± 43	3
5				18 ± 4	2	12 ± 2	3
Ro 25- 6981				159 ± 29	3	6 ± 1	3
CI-1041				6.6 ± 1.2	3	4 ± 1	3

In vitro biological activity of the prepared compounds was measured in a binding assay on rat forebrain membrane using tritiated Ro-25,6981 as radioligand and in a functional assay where the inhibition of NMDA-evoked increase of intracellular Ca²⁺ level was determined on rat cortical cell culture.

In vivo analgesic activity was tested in the mouse formalin test, a model of persistent pain.

Based on the results obtained, the authors concluded: new benzimidazole-2-carboxamides found to be potent selective antagonists of the NR2B subtype of NMDA receptors; Compound **6a** has shown excellent analgesic activity in the mouse formalin test following oral administration.