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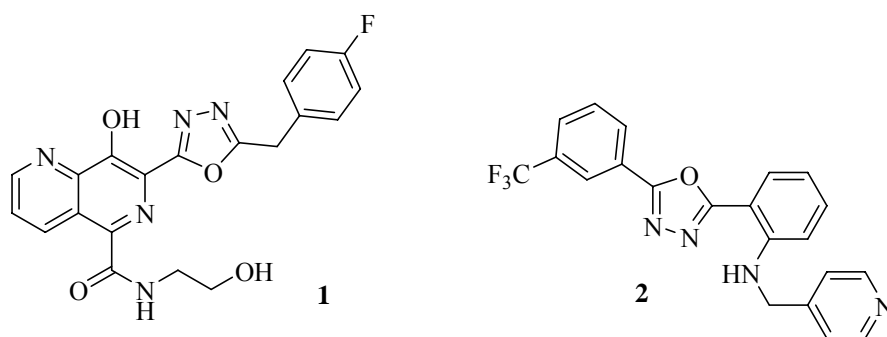
Abstract: *The 39th Middle Atlantic Regional Meeting of the American Chemical Society: MARM 2007 was held in Collegeville, PA. This report covers various material presented at the conference of relevance to medicinal and synthetic chemistry and biochemistry.*

“Discovery of Non-Transition-State Isostere BACE Inhibitors,”

Hemaka A. Rajapakse, (Merck Research Laboratories), West Point, PA

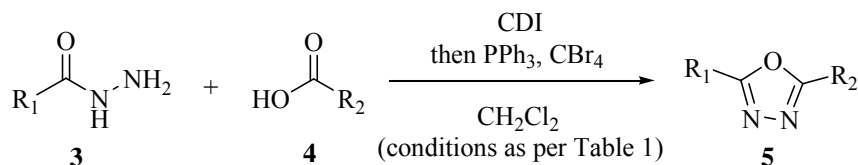
In this presentation Hemeka Rajapakse reported on the discovery of BACE-1 inhibitors as potential candidates for the treatment of Alzheimer’s Disease as well as a mild one pot synthesis of 1,3,4-oxadiazoles as BACE-1 inhibitors. Many BACE-1 inhibitors have failed to make it into therapeutic treatment for Alzheimer’s disease because, though potent, they are unable to permeate the central nervous system. Rajapakse presents a novel aspartyl protease binding motif with improved central nervous system penetration, as well as its impact at the catalytic site of BACE-1.¹

Figure 1



Shown above are 2 synthetic 1,3,4-oxadiazoles (Figure 1). Compound 1 is used for HIV integrase inhibition and compound 2 is an angiogenesis inhibitor. The synthetic route for creation of 1,3,4-oxadiazoles is typically a 2-step process where the acylhydrazine and carboxylic acid are coupled under amide bond forming conditions, then purified and dehydrated with standard reagents. Merck scientists have come up with an effective and mild way to make the 1,3,4-oxadiazoles in one pot as presented below (Scheme 1).

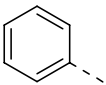
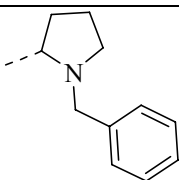
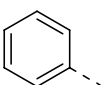
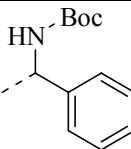
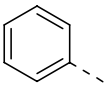

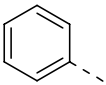
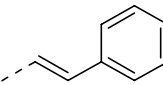
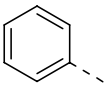
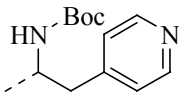
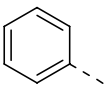
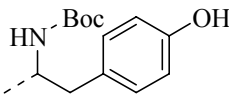
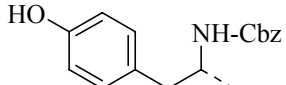

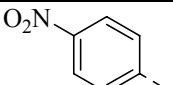

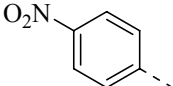
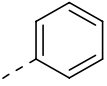
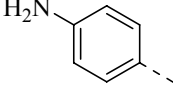
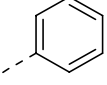
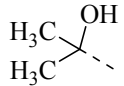
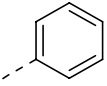
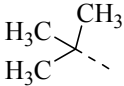
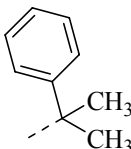
Scheme 1



Many variations of each the carboxylic acid and the hydrazide were investigated as shown in Table 1. Along with the time saved by modifying this reaction into a one pot process, it was also observed that strictly anhydrous conditions were not required. In addition the intermediate was readily observable by TLC or LC/MS and no aqueous work up was necessary for the final products which were purified using normal phase chromatography.

¹ H. A. Rajapakse et al. *J. Med. Chem.* **2006**, *49*, 7270-7273.

Table 1. Yields, conditions and structural variations of compounds **5a-l**.

Product	R ₁	R ₂	Conditions	Yield (%)
5a			RT	52
5b			RT	66
5c			RT	73
5d			Coupling heated to 40°C	23
5e			Coupling intermediate not detected by LC/MS	0
5f			Coupling intermediate not detected by LC/MS	0
5g			RT	90
5h			RT	75
5i			Coupling heated to 40°C	54
5j			Coupling heated to 40°C	37
5k			RT, 15h	62
5l			Solvent: ClCH ₂ CH ₂ Cl, coupling heated to 70°C, dehydrated at RT	62

The only functionality studied that failed to work by this methodology was in the case where a nucleophilic group was present on the carboxylic acid (see **5e** & **5f**, Table 1). Noteworthy in this

series is **51** that included sterically demanding partners on both the carboxylic acid and the hydrazine and was found to have comparable yield to less hindered reactions.

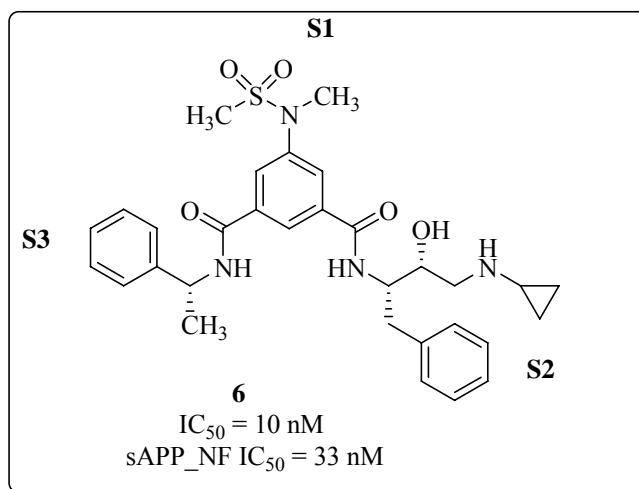
Along with structural variation, Merck researchers also studied the effects of changing solvents, temperatures and protecting groups as shown in Table 2.²

Table 2. Solvent, temperature and protecting group effects

Solvent	Temperature (°C)	Yield (%)	Protecting Group (PG)	Yield (%)
CH ₂ Cl ₂	0	83	Boc	83
CH ₂ Cl ₂	RT	87	Cbz	81
CH ₂ Cl ₂	0→RT	75	Ac	75
THF	0→RT	50	Fmoc	73
DMF	RT	0	TFA	57

Merck's scientists applied this one pot methodology to the discovery of an oxadiazoyl tertiary carbinamine inhibitor of BACE-1. They took a well known intrinsically and functionally active hydroxyethylamine derived inhibitor (**6**) of BACE-1 and tried to modify it to maintain activity but improve penetration and reduce the number of hydrogen bond donors and acceptors so as to be less susceptible to efflux by P-glycoprotein and improve central nervous system penetration without loss of potency.³

Figure 2



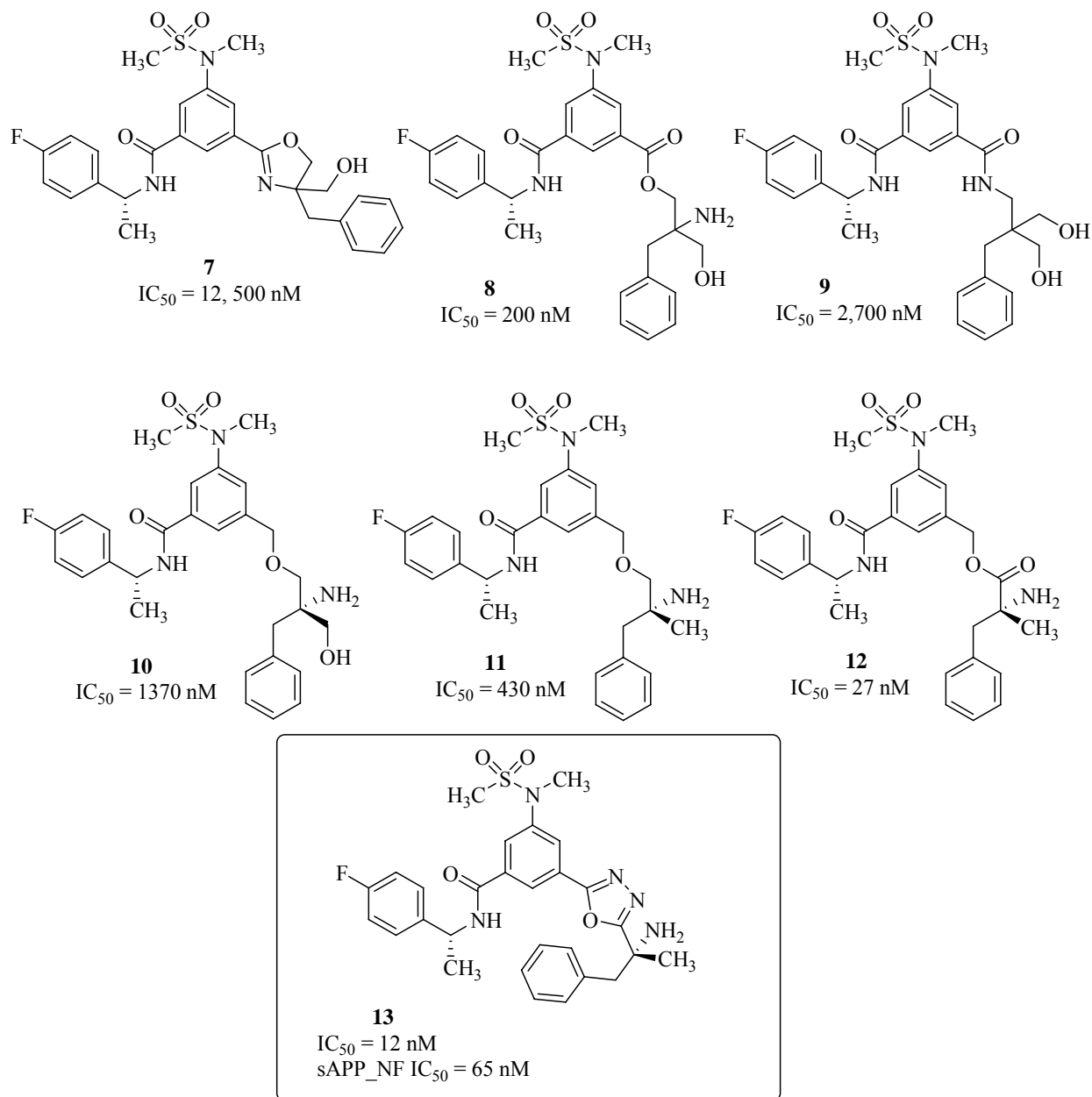
After many variations of all three binding sites Merck could not find a better **S1** site modification, **S3** was modified to include a fluorine in the para position of the phenyl ring and the best replacement they found to date for the **S2** position included a 1,3,4-oxadiazole moiety. Compounds **7-13** show a sampling of the SAR results. Compound **13** has very comparable SAR, is more rigid and has less hydrogen bonding characteristics than the literature compound **6**.

² H. A. Rajapakse et al. *Tetrahedron Letters*, **2006**, 47, 4827-4830.

³ H. A. Rajapakse et al. *J. Med. Chem.* **2006**, 49, 7270-7273.

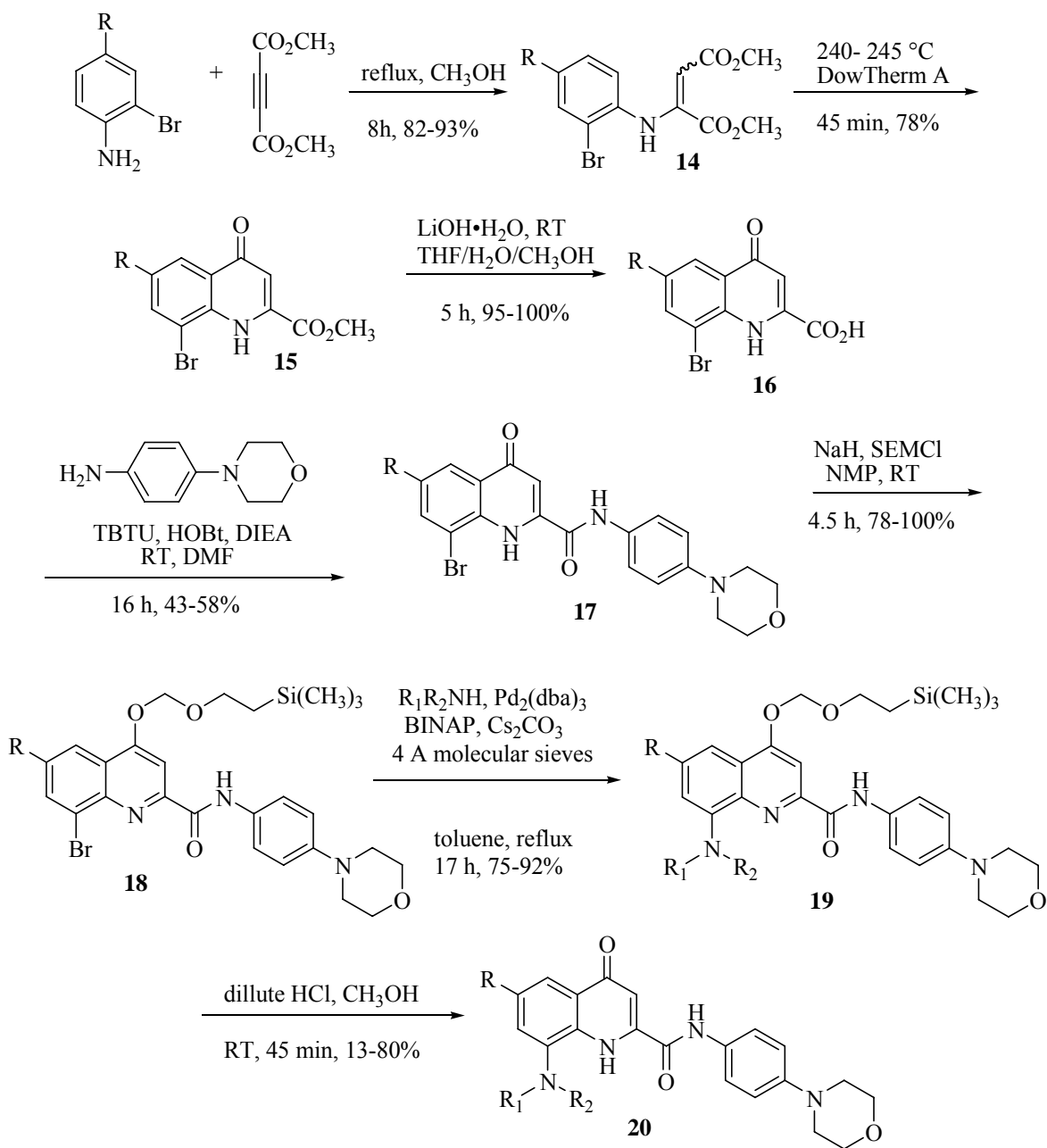
Sadly, the P-gp assay of compound **13** predicts that it will not be a brain penetrating compound. Finding a better central nervous system penetration moiety is an ongoing effort by this group.

Figure 3



“Synthesis of Novel Quinolone and Quinoline-2-carboxylic acid(4-morpholin-4-yl-phenyl)amides: A Late-Stage Diversification Approach to Potent 5HT_{1B} Antagonists,”
Carey L. Horchler, (AstraZeneca Pharmaceuticals), Wilmington, DE.

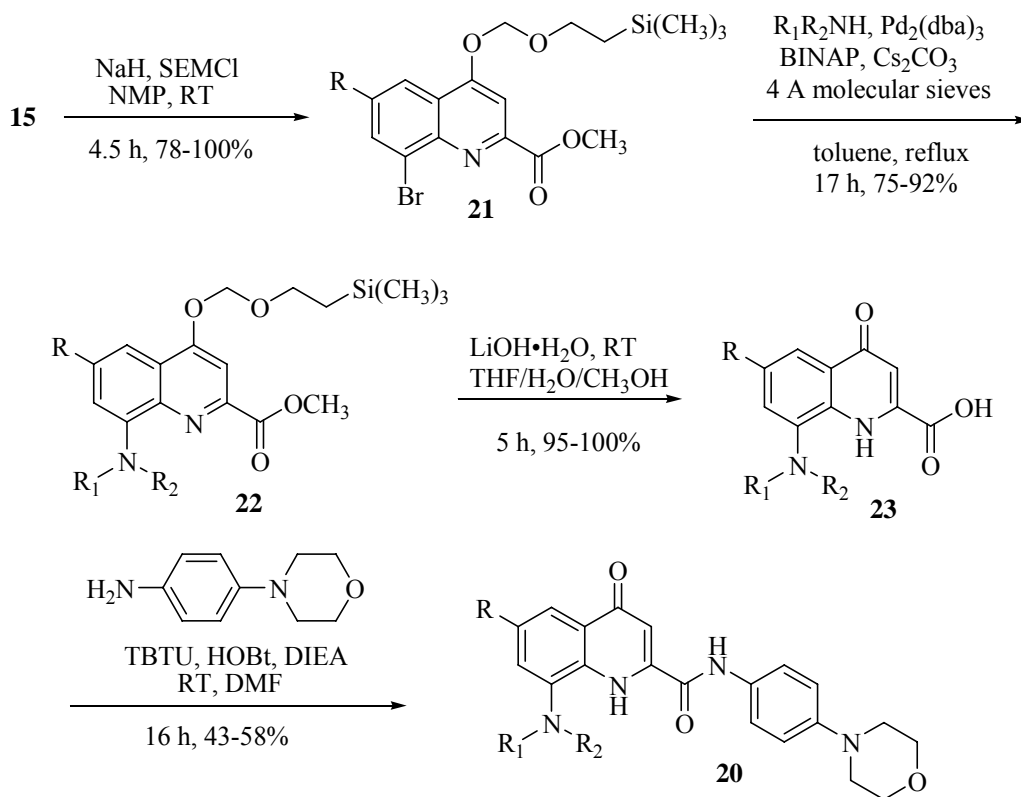
Scheme 2



Scheme 2 shows the primary synthetic route to the active quinolones made from commercially available starting materials (where R = OCH_3).

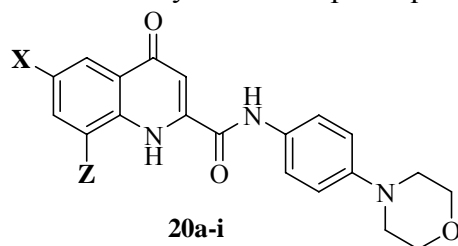
In this presentation Horchler discussed the synthesis and preliminary SAR data of potent 5HT_{1B} antagonists. Compounds that are 5HT_{1B} antagonists may help alleviate depression, anxiety and migraines. She detailed a late stage diversification syntheses of quinolone and quinoline-2-carboxylic acid(4-morpholin-4-yl-phenyl)amide analogs.⁴

Scheme 3



Scheme 3 details an alternative order of the synthetic route where R = F. Preliminary SAR of this series is presented in Table 3.

⁴ C. L. Horchler et al. *Bioorg. Med. Chem.* **2007**, *15*, 939-950.

Table 3. Structure-activity relationships of quinolones **20a-i**.

Compound	X	Z	K _i ^a (nM)	Yield (%)
20a	OCH ₃		0.9	81
20b	OCH ₃		292	79
20c	OCH ₃		3.5	85
20d	OCH ₃		392	78
20e	OCH ₃		35	100
20f	OCH ₃		>1000	100
20g	OCH ₃		170	100
20h	OCH ₃		>1000	50
20i	F		9.3	88

Scheme 4 details the route from quinolone **16** to the late stage diversification of the quinolones series. Preliminary SAR data of analogs **26a-c** is presented in Table 4.

Scheme 4

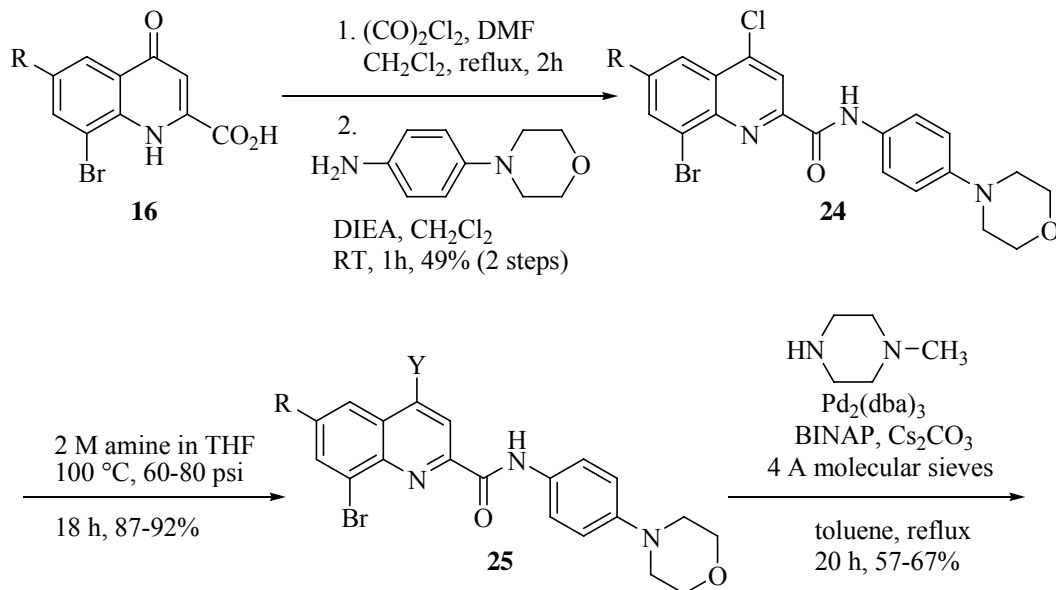
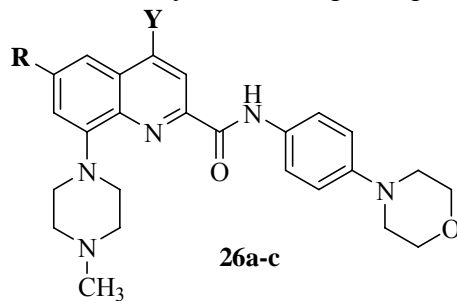


Table 4. Structure-activity relationships of quinolines **26a-c**.



Compound	R	Y	K_i^a (nM)	Yield (%)
26a	OCH ₃	N(CH ₃) ₂	51	67
26b	OCH ₃	NHCH ₃	1300	57
26c	F	OCH ₃	30	90

In conclusion, AstraZeneca's scientists have gotten a good start on diversification of quinolones and quinolines and have found that the order of the synthetic steps can be changed (such as when the amide coupling with 4-morpholinoaniline occurs). This series also shows that the chirality of the product can greatly influence the SAR (as demonstrated by compounds **20e** and **20f**). This SAR also suggests that many other amines could show similar effects to the traditional piperazine side chain.