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Bioorganic & Medicinal Chemistry Letters 14 (2004) 445–448
Bioorganic & Medicinal Chemistry Letters

1,2-Diaryl-1-ethanone and pyrazolo [4,3-*c*] quinoline-4-one as novel selective cyclooxygenase-2 inhibitors☆

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Received 9 May 2003; accepted 25 October 2003

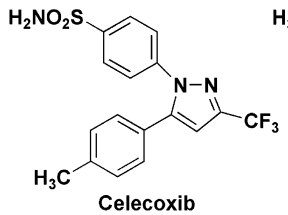
Abstract—Novel 1,2-diaryl-1-ethanone **1** and pyrazolo [4,3-*c*] quinoline-4-one **2**, with pharmacophores different from the known COX inhibitors were identified as selective COX-2 inhibitors. The communication briefly describes SAR of both the series.

The recent years have witnessed increased interest in developing potent and selective cyclooxygenase-2 (COX-2) inhibitors that could reduce pain and inflammation without affecting the cyto-protective action of cyclooxygenase-1 (COX-1)[1]—the site of action for all the classical NSAIDS. This has led to the discovery of a novel class of drugs, such as rofecoxib[2,3] and celecoxib,[4] that are currently marketed for the treatment of arthritis or pain relief in humans. There is an ongoing effort to develop second generation COX-2 inhibitors, structurally different from the existing ones. A perusal of literature reveals that structural diversity exists in the chemical scaffolds of COX-2 inhibitors.[5]

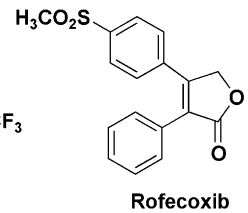
In pursuance of our research for the development of novel COX-2 inhibitors,[6,7] we were interested in developing 1,2-diaryl-1-ethanone **1** and pyrazolo [4,3-*c*] quinoline-4-one **2** as novel pharmacophores for selective COX-2 inhibition and wish to report our preliminary results in this communication. Compounds **1** and **2** can be visualized as precursors as well as fused forms of the well known tri-aryl heterocycles.

Compounds **1** were prepared as outlined in Scheme 1.

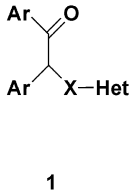
The synthetic route is based on conventional Friedel–Craft acylation reaction. The substituted phenacyl chlorides were treated with substituted aryl compounds in presence of $AlCl_3$ using dichloromethane as solvent. After usual workup, the required di-aryl ethanones were obtained in almost quantitative yield. The di-aryl ethanones were then treated with Br_2 in CCl_4 to give 1-bromo-2-ethanone derivatives which were condensed with different substituted heterocycles to give compounds **1** (Table 1).



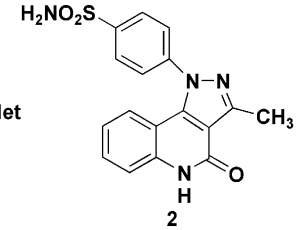
Celecoxib



Rofecoxib



1



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☆DRL Publication No. 281-A.

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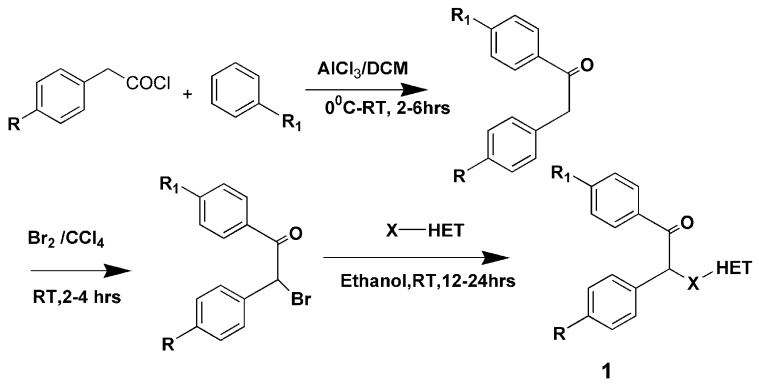
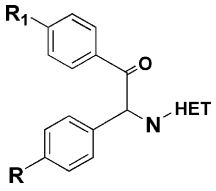
doi:10.1016/j.bmcl.2003.10.052



Scheme 1.

Table 1. In vitro data for 1,2-diaryl-1-ethanones



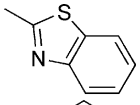
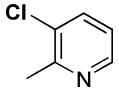
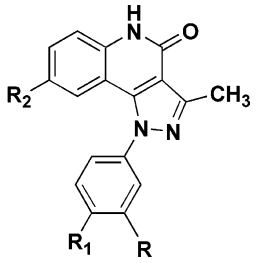
S. no.	R_1	R	Heterocycle	In vitro biological activity	
				Cox-1 (10 μM)	Cox-2
1a	$SOCH_3$	H		29	93
1b	SO_2CH_3	H		10	83
1c	F	$SOCH_3$		0	93
1d	F	SO_2CH_3		0	83
1e	F	SO_2NH_2		23	61
1f	F	SO_2NH_2		0	60
1g	F	SO_2NH_2		30	92
1h	F	SO_2NH_2		0	75
1i	F	$SOCH_3$		0	100
1j	SCH_3	H		53	100

Table 2. In vitro data for pyrazolo[4,3-*c*] quinolones

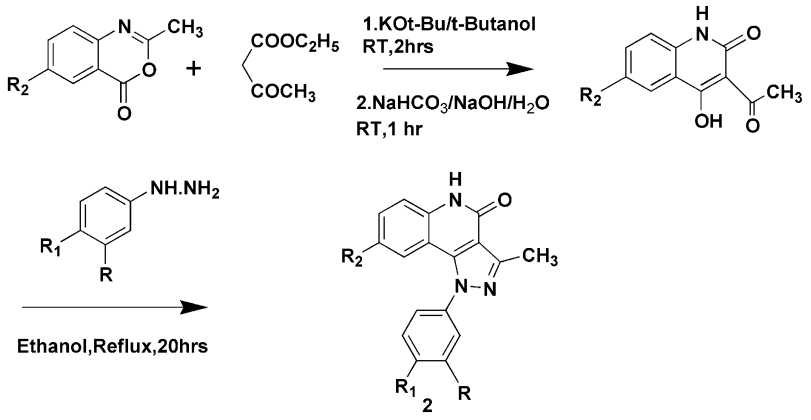


S. no	R	R_1	R_2	In vitro biological activity	
				Cox-1 (10 μM)	Cox- 2
2a	H	H	H	82	4
2b	CH_2OH	SO_2NH_2	H	0	50
2c	H	SO_2NH_2	H	20	90
2d	H	SO_2NH_2	NO_2	40	100
2e	H	SO_2NHCH_2Ph	NO_2	78	36
2f	H	H	NO_2	46	100
2g	CH_2OH	SO_2NH_2	NO_2	0	30

Similarly, compounds **2** were prepared as described in Scheme 2.

The substituted isatoic anhydride derivatives prepared from the corresponding anthranilic acid and acetic anhydride following standard literature methods[8] were treated with ethyl acetoacetate in presence of potassium *t*-butoxide and *t*-butanol to give the substituted quinolones. The quinolones were then treated with substituted hydrazine in ethanol under reflux in N_2 atmosphere, resulting in required pyrazolo quinoline-4-one compounds **2** (Table 2).

All the compounds[9] were tested for COX-1 and COX-2 inhibition by spectrophotometric method, as reported in literature.[10] Microsomal fraction of ram seminal vesicles was used as a source of COX-1 enzyme and microsomes from sf-9 cells infected with baculovirus expressing human COX-2 cDNA was used as a source of COX-2 enzyme. Enzymatic activity was measured using a chro-



Scheme 2.

mogenic assay based on oxidation of *N*,*N*,*N*,*N*-tetramethyl-*p*-phenylenediamine (TMPD) during the reduction of PGG_2 to PGH_2. The assay mixture (1000 μL) contained 100 μM Tris pH 8.0, 3 μM EDTA, 15 μM hematin, 150 units enzyme and 8% DMSO. The mixture was incubated at 25 °C for 15 min before initiation of enzyme reaction in presence of compound/vehicle. The reaction was initiated by the addition of 100 μM arachidonic acid and 120 μM TMPD. The enzyme activity was measured by estimation of the initial velocity of TMPD oxidation over the first 25 s of the reaction followed from the increased in absorbancy at 603 nm. The IC_{50} values were calculated using non-linear regression analysis of percentage inhibition.

As can be readily understood from Table 1, in the diaryl-1-ethanone series **1**, COX-2 selectivity mainly depends on the substituent on both the aryl ring as well as on the heterocycles. When the sulfonyl or sulfanyl group is in 1-aryl ring, selectivity decreases though it inhibits both COX-1 and COX-2. But when these groups are shifted to 2-aryl ring, the selectivity changes dramatically. The selectivity also depends on the substituted heterocycles. Thus, in this series, we were able to get selective inhibitors like **1c** ($IC_{50} = 500$ μM for COX-1 and 2.1 μM for COX-2) and **1i** ($IC_{50} = 50$ μM for COX-1 and 0.5 μM for COX-2).

In series **2**, when R, R_1, R_2 are only H, the compounds are more COX-1 selective whereas when R_2 is replaced by NO_2 and R_1 by sulfonamide group, the selectivity is more towards COX-2. By synthesizing a limited number of compounds, we were able to identify few highly active and selective COX-2 inhibitors like **2d** ($IC_{50} = 4.7$ μM for COX-1 and 0.24 μM for COX-2) and **2f** ($IC_{50} = 5.0$ μM for COX-1 and 0.55 μM for COX-2). All the four compounds were showing activity in the range of 25–45% in Carrageenan induced rat paw model at 30 mg/Kg.[11]

In conclusion, 1,2-diaryl-1-ethanones **1c** and **1i** and pyrazolo [4,3-*c*] quinoline-4-one **2d** and **2f** were identified as selective COX-2 inhibitors. The results presented here indicate that the two novel series may serve as alternative pharmacophores.

Acknowledgements

The authors thank analytical department, Dr. A. Venkateswarlu and Dr. R. Rajagopalan for their support and discussions.

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11. Details will be published elsewhere in a full paper.