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Discovery of novel, non-acidic 1,5-biaryl pyrrole EP_1 receptor antagonists

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Abstract—Replacement of the carboxylic acid group in a series of previously described 1,5-biaryl pyrrole EP_1 receptor antagonists led to the discovery of various novel non-acidic antagonists. Several analogues displayed high binding affinity and high binding efficiency indices.

Prostaglandin E_2 (PGE_2), Figure 1, is a lipophilic, 20-carbon atom, carboxylic acid. It is synthesized in vivo from arachidonic acid by the sequential action of cyclo-oxygenase (COX) and prostaglandin E synthase (PGES) enzymes.[1] PGE_2 is known to activate four 7-transmembrane (TM) G-protein coupled receptors, EP_{1-4}.[2]

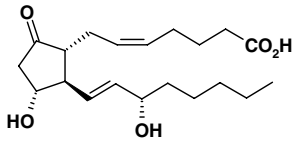

Figure 1. Prostaglandin E_2 (PGE_2).

It has been postulated that the carboxylic acid, present in all prostanoid ligands, forms a key binding interaction (salt bridge) with a highly conserved arginine residue, present on TM-7 of all the prostanoid receptors.[2a] Hence, most of the known ligands for the prostanoid receptors contain acidic groups which are essential to bind to the receptor.[1,3] We, and others, have described acidic EP_1 receptor antagonists,[4–8] however, to date only three non-carboxylic acid based templates have been described, exemplified by SC-51322 (**1**)[9] and analogues[10] from Searle and **2**[11] and **3**[6] from Merck Frosst, Figure 2. Progress in this area has been stifled due to difficulties such as escalating molecular weight which leads to a lower binding efficiency index (BEI).[12] For example, compound **2** has a pK_i of 7 and its molecular weight is 620 Da which gives a BEI of 11.2. Acidic ligands, on the other hand, have high affinity,

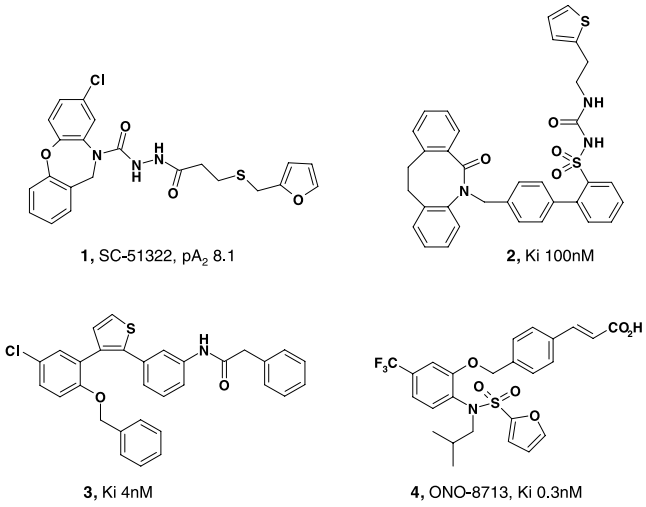

Figure 2. Selection of non-carboxylic acid based EP_1 antagonists and ONO-8713.

Keywords: EP_1 antagonist; Pyrrole; Carboxylic acid replacement.
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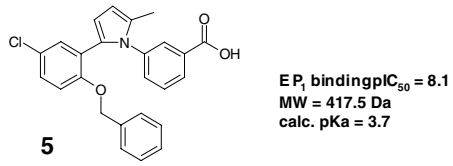


Figure 3. Profile of lead compound **5**.

for example ONO-8713 (**4**) has a K_i of 0.3 nM[7] with a molecular weight of 471 Da which gives a BEI of 20.2.

Compound **5**,[4] Figure 3, exhibits a binding pIC_{50} of 8.1 and has a MW of 417.5 Da, therefore giving a BEI of 19.4.

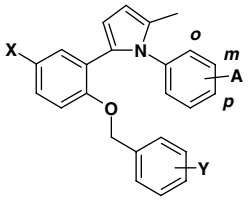
Due to the paucity of known non-acidic EP_1 receptor antagonists, we were interested in assessing whether the carboxylic acid moiety could be replaced by non-acidic groups and what effect this change would have on in vitro affinity.

Based on the facile synthesis of 1,5-biaryl pyrroles, such as **5**, Figure 3, we felt this template offered the potential to identify novel, lower molecular weight non-acidic antagonists by utilizing array chemistry. Thus, Paal–Knorr condensation[13] of a 1,4-diketone with readily available anilines would allow a high-throughput assessment of novel carboxylic acid-replacement groups.

Compound activities were determined in a [^{3}H]-PGE_2 binding assay at the recombinant human EP_1 receptor expressed in CHO cell membranes.[4,5b,14]

Before commencing work with non-acidic groups we first sought to profile some biosteric carboxylic acid replacements such as acylsulfonamides and tetrazoles, Table 1.

Table 1. SAR and calcd pK_a values for biosteric carboxylic acid replacements



Compound	X	Y	A	pIC_{50}[a]	Calcd pK_a[b]
5	Cl	H	*m*-CO_2H	8.1 ± 0.4	3.70
6a	Br	2,4-DiF	*m*-$CONHSO_2Me$	8.4 ± 0.1	3.27
6b	Cl	H	*m*-$CONHSO_2Ph$	8.6 ± 0.3	3.85
6c	H	H	*m*-$CONHSO_2Ph$	8.6 ± 0.2	3.85
6d	H	H	*m*-$CONHSO_2$isox[c]	8.3 ± 0.2	2.88
6e	Cl	H	*m*-$SO_2NHCOPh$	7.1 ± 0.2	3.40
6f	Cl	H	*p*-$SO_2NHCOPh$	8.1 ± 0.2	3.60
6g	Br	2,4-DiF	*m*-Tetrazole	8.2 ± 0.2	3.81
6h	Br	2,4-DiF	*p*-$C(CF_3)_2OH$	7.6 ± 0.3	8.79

[a] Values are means of at least three experiments.
[b] Calculated pK_a values using ACD software version 8.0.
[c] isox, 3,5-dimethylisoxazol-4-yl.

The results in Table 1 show that the *meta*-acylsulfonamides, **6a**–**d**, retained the activity of the carboxylic acid **5**, and affinity was not influenced by the functionality on the left-hand side of the molecule (X-group or the benzyloxy group). This indicated that sterically demanding groups such as phenyl could be incorporated in the acylsulfonamide, that is, in the acid binding region. Reversal of the acylsulfonamide at the *meta*-position, **6e**, was tolerated, albeit with a considerable decrease in activity. However, translocation of the reversed acylsulfonamide from the *meta*- to the *para*-position, **6f**, restored activity. The tetrazole **6g** was also well tolerated.[15] Pleasingly, the hexafluoropropan-2-ol derivative **6h** displayed good activity, despite having a considerably higher calculated pK_a (8.79). The calculated pK_a compares well with reported pK_a values (8.5) for similar compounds containing this group.[16a]

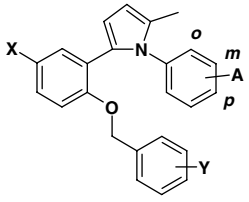
When compared to recent results from Merck Frosst where a similar analogue (related to **3**), with hexafluoropropan-2-ol group in the *meta*-position, had a K_i of 260 nM[6] our results demonstrate that this group shows higher activity when located at the *para*-position.

Based on the calculated pK_a data for **6h** we felt that the hexafluoropropan-2-ol group could potentially form a hydrogen bond with the receptor, rather than an ionic interaction. This hypothesis is supported by recent crystallographic data for a LXR receptor ligand containing the hexafluoropropan-2-ol group, where this moiety forms hydrogen bonds with histidine and tryptophan residues.[16b]

Hence, we sought to replace the carboxylic acid with hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) groups in the *meta*- and *para*-positions of the phenyl ring.

In the first instance we prepared the *meta*- and *para*-sulfones and sulfonamides as these groups have HBA and HBA/HBD potential, respectively, Table 2. In addition these groups have been found to bind to the arginine res-

Table 2. SAR of sulfone and sulfonamide carboxylic acid replacements



Compound	X	Y	A	pIC_{50}[a]
7a	H	H	*m*-SO_2Me	<6
7b	Cl	H	*m*-SO_2Me	6.9 ± 0.1
7c	Br	H	*m*-SO_2Me	6.7 ± 0.2
7d	H	H	*p*-SO_2Me	6.3 ± 0.1
7e	Cl	H	*p*-SO_2Me	7.7 ± 0.1
7f	Br	H	*p*-SO_2Me	7.5 ± 0.2
7g	Cl	H	*p*-SO_2NH_2	7.7 ± 0.2

[a] Values are means of at least three experiments.

idue in the COX-2 enzyme,[17] thus we hypothesized that they may be able to form a similar interaction with the arginine residue in the EP_1 receptor.

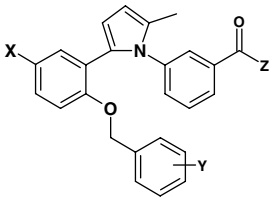
The *meta*-sulfones had low affinity, **7a**–**c**. However, the *para*-sulfones showed good activity, although it was found that a halogen such as Cl, **7e**,[18] or Br, **7f**, was necessary on the left-hand side phenyl ring. Similarly, the primary sulfonamide, **7g**, also showed good activity when located at the *para*-position. These initial results implied the HBA ability of the new functionality was important.

Furthermore, these results compare well with recent data published by Merck Frosst on a related 2,3-biarylthiophene template (related to **3**), where a *meta*-sulfonamide was found to display similar affinity to the corresponding carboxylic acid.[6]

Encouraged by our preliminary investigations, we synthesized several *meta*-amide derivatives, Table 3.[19]

The primary amides **8a** and **b** displayed encouraging activity; however, their activity appeared to be heavily influenced by the interactions formed by the left-hand side of the molecule. Thus, activity could be improved when X was halogen. Investigation of further substituted derivatives, **8c**–**e**, indicated that the amide could be substituted and the activity of the dimethyl amide **8d** suggested that the amide was acting as a hydrogen bond acceptor (HBA). Although the anilide **8e** had significantly lower activity, we synthesized the benzyl amide **8f** as this compound can be viewed as an analogue of **6b**, where the SO_2 moiety has been replaced by a methylene group, thus the compound has similar steric demands but is no longer acidic. Pleasingly **8f** demonstrated good affinity with an IC_{50} of 25 nM (pIC_{50} 7.6). The phenyl group of the benzyl amide could be replaced by pyridine, **8g**–**i**, with little effect on activity. Furthermore, the benzylic position could be substituted, although this position was sensitive to the stereochemistry, **8j**–**k**. Again, results correspond with recent observations in a related series.[6]

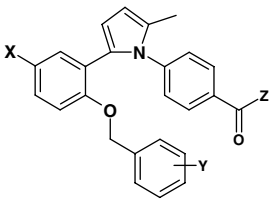
Table 3. SAR of the *m*-amide derivatives



Compound	X	Y	Z	pIC_{50}[a]
8a	H	2,4-DiF	$-NH_2$	6.3 ± 0.2
8b	Cl	H	$-NH_2$	7.2 ± 0.2
8c	Br	2,4-DiF	–NHMe	7.7 ± 0.1
8d	Br	2,4-DiF	$-NMe_2$	8.0 ± 0.2
8e	Br	2,4-DiF	–NHPh	6.3 ± 0.2
8f	Cl	H	$-NHCH_2Ph$	7.6 ± 0.4
8g	Cl	H	$-NHCH_2$-(2-pyridyl)	7.3 ± 0.3
8h	Cl	H	$-NHCH_2$-(3-pyridyl)	7.2 ± 0.3
8i	Cl	H	$-NHCH_2$-(4-pyridyl)	7.2 ± 0.2
8j	Cl	H	(*S*)-NHCH(Me)Ph	6.5 ± 0.2
8k	Cl	H	(*R*)-NHCH(Me)Ph	7.4 ± 0.1

[a] Values are means of at least three experiments.

Table 4. SAR of the *p*-amide derivatives



Compound	X	Y	Z	pIC_{50}[a]
9a	Br	2,4-DiF	$-NH_2$	8.1 ± 0.3
9b	Br	2,4-DiF	–NHMe	8.4 ± 0.1
9c	Br	2,4-DiF	$-NMe_2$	7.8 ± 0.2
9d	Br	2,4-DiF	$-NEt_2$	7.3 ± 0.2
9e	Br	2,4-DiF	–NH*t*-Bu	7.8 ± 0.1
9f	Cl	H	$-NHCH_2Ph$	7.6 ± 0.2
9g	Cl	H	$-NHCH_2$-(2-pyridyl)	8.6 ± 0.3
9h	Cl	H	$-NHCH_2$-(3-pyridyl)	7.9 ± 0.3
9i	Cl	H	$-NHCH_2$-(4-pyridyl)	7.2 ± 0.2
9j	Cl	H	(*S*)-NHCH(Me)Ph	8.3 ± 0.1
9k	Cl	H	(*R*)-NHCH(Me)Ph	8.8 ± 0.1

[a] Values are means of at least three experiments.

Based on the results for the acylsulfonamides, we sought to ascertain if the amide could be moved from the *meta* to the *para*-position, Table 4.[20]

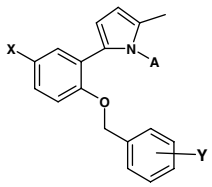
Results in Table 4 show that the *para*-amides displayed similar activity to their analogous *meta*-counterparts, and in some instances actually displayed higher activity, **8g** versus **9g**. It was also found that the substitution of the benzylic carbon atom was less sensitive to stereochemistry than in the *meta*-amide series, **9j**–**k**.

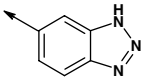
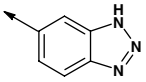
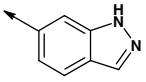
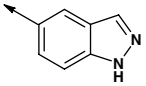
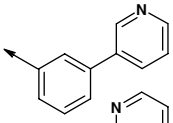
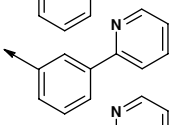
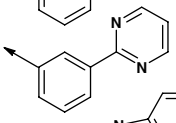
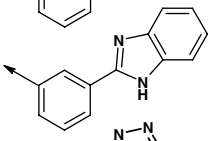
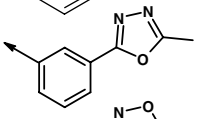
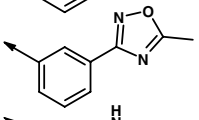
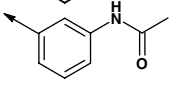
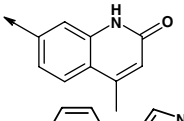
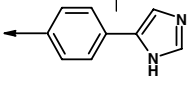
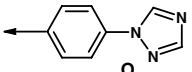
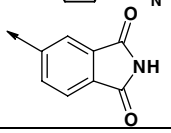
Due to the insight gained from the SAR in the amide and sulfone/sulfonamide series, we synthesized compounds that contained a heterocycle or fused heterocycle that could form a HBA and/or HBD interaction with the receptor. Representative examples from this series are summarized in Table 5.[21,22]

Several derivatives displayed encouraging affinity. Notably, the most active derivatives contained both HBA and HBD groups, with the exception of oxadiazole **10i** which showed higher affinity than other derivatives with only HBA functionality. This is contrary to the results in the amide and sulfone series, where the HBA interaction appeared predominant. Of note are the benzotriazole **10b**, indazoles **10c** and **10d**, benzimidazole **10h**, the oxadiazole **10i** and the imidazole **10m**. These results demonstrate the feasibility of replacing the carboxylic acid with novel non-acidic groups. The reversed amide derivatives, **10k** and **10l** (where the amide group is reversed with respect to the amides derived from the carboxylic acid) also displayed good affinity, Table 5.

Compounds were synthesized as shown in Schemes 1–3. Full experimental procedures and characterizing data

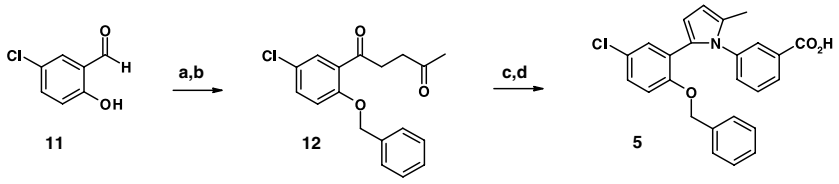
Table 5. SAR of various novel carboxylic acid replacements



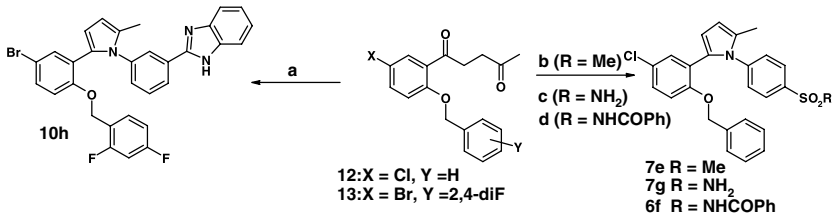
Compound	X	Y	A	pIC_{50}[a]
10a	H	2,4-DiF		6.2 ± 0.1
10b	Cl	H		7.6 ± 0.2
10c	Cl	H		7.4 ± 0.3
10d	Cl	H		7.4 ± 0.2
10e	Br	2,4-DiF		6.9 ± 0.2
10f	Br	2,4-DiF		6.6 ± 0.1
10g	Br	2,4-DiF		6.9 ± 0.1
10h	Br	2,4-DiF		7.2 ± 0.1
10i	Br	2,4-DiF		7.4 ± 0.1
10j	Br	2,4-DiF		6.7 ± 0.1
10k	Cl	H		7.2 ± 0.1
10l	Cl	H		7.2 ± 0.3
10m	Br	2,4-DiF		7.4 ± 0.1
10n	Cl	H		6.3 ± 0.1
10o	Br	2,4-DiF		6.8 ± 0.1

[a] Values are means of at least three experiments.

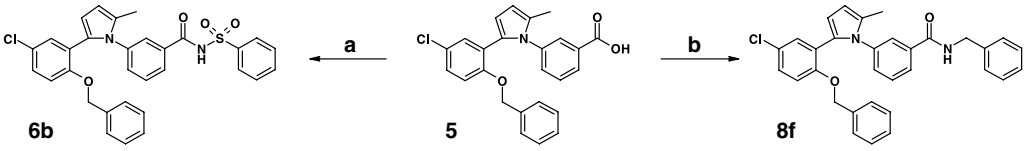
for key compounds have been published.[5] The starting salicylaldehydes were commercially available. Alkylation of 5-chlorosalicylaldehyde **11** gave the corresponding *O*-benzylsalicylaldehyde. Stetter reaction[23] with methylvinylketone (MVK) yielded the corresponding 1,4-diketone **12**. Paal–Knorr condensation[13] with



Scheme 1. Reagents and conditions: (a) BnBr, DMF, K_2CO_3, 60 °C, 100%; (b) MVK, TEA, EtOH, 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide, reflux, 81%; (c) ethyl 3-aminobenzoate, PhMe, pTSA, reflux, 60%; (d) 2 M NaOH, EtOH, reflux, 100%.



Scheme 2. Reagents and conditions: (a) **13**, 1H-(benzimidazol-2-yl)-phenylamine, pTSA, PhMe, reflux, 53%; (b) **12**, 4-(methylsulfonyl)aniline hydrochloride, TEA, PhMe, reflux, 50%; (c) **12**, sulfanilamide, pTSA, PhMe, reflux; (d) **12**, sulfabenzamide, pTSA, PhMe, reflux, 72%.



Scheme 3. Reagents and conditions: (a) $PhSO_2NH_2$, CDI, DIPEA, DCM, rt, 44%; (b) $PhCH_2NH_2$, EDC, HOBt, DCM, rt, 58%.

anilines (refluxing PhMe in the presence of pTSA) gave the desired products as outlined in Scheme 1. Alternatively, the condensation reaction could be carried out under microwave irradiation (in NMP, with a catalytic amount of pTSA, 150 °C, 15 min) to yield the desired products. The anilines were generally commercially available, or were prepared as described.[5,6] The reverse acylsulfonamides, for example **6f**, were prepared directly via condensation with sulfabenzamide, Scheme 2. Acylsulfonamides such as **6b** were prepared from the corresponding carboxylic acid, Scheme 3. Several anilines were available with amides already installed. Alternatively, the amides could be prepared from the carboxylic acid under standard conditions, for example, **8f**, Scheme 3.

In conclusion, we have discovered several potent non-acidic EP_1 receptor antagonists. We have shown that the substitution on the left-hand side of these molecules has a greater influence on activity than in the corresponding carboxylic acid series. Furthermore, we have described the first non-acidic antagonists for the EP_1 receptor with high binding efficiency indices (BEIs), such as compound **7g** with a BEI of 17.0 and **9g** with a BEI of 16.9. Several interesting heterocyclic replacements were also discovered, such as the benzimidazole derivative **10h** and the imidazole **10m**.

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14. Data from the [^{3}H]PGE_2 binding assay are quoted as pIC_{50} values. These data can be converted to pK_i values by subtracting 0.04 from the pIC_{50} values.
15. In vitro metabolic stability data (intrinsic clearance, CLi) for compounds **6a**, **6c** and **6h** in rat and human liver microsomes: **6a** rat CLi 2.7 mL/min/g liver, human CLi 5.4 mL/min/g liver; CYP450 IC_{50} values all >10 μM at 1A2, 2C19, 2D6 and 3A4 isoforms, IC_{50} = 0.63 μM at the 2C9 isoform; **6b** rat CLi 3.1 mL/min/g liver, human CLi 5.2 mL/min/g liver; **6c** rat CLi 8.8 mL/min/g liver, human CLi 6.5 mL/min/g liver; **6f** rat CLi 6.7 mL/min/g liver, human CLi 3.4 mL/min/g liver; **6h** rat CLi 3.5 mL/min/g liver, human CLi 0.8 mL/min/g liver.
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18. Compound **7e** displayed a half-life of 2.1 h when administered intravenously to male Sprague–Dawley rats at a dose of 1 mg/kg. CYP450 IC_{50} values ⩾10 μM at 1A2, 2C9, 2D6 and 3A4 isoforms, IC_{50} = 5.0 μM at 2C19 isoform.
19. In vitro metabolic stability data (intrinsic clearance, CLi) for compounds **8b**, **8d**, **8f** and **8g** in rat and human liver microsomes: **8b** rat CLi 39.0 mL/min/g liver, human CLi 25.0 mL/min/g liver; **8d** rat CLi >50.0 mL/min/g liver, human CLi >50.0 mL/min/g liver, CYP450 IC_{50} values ⩾10 μM at 1A2 and 2D6, the 2C19, 2C9 and 3A4 isoforms displayed IC_{50} values between 1 and 6 μM; **8f** rat CLi 42.0 mL/min/g liver, human CLi >50.0 mL/min/g liver; **8g** rat CLi >50.0 mL/min/g liver, human CLi >50.0 mL/min/g liver.
20. In vitro metabolic stability data (intrinsic clearance, CLi) for compounds **9a**, **9b**, **9f**, **9g** and **9k** in rat and human liver microsomes: **9a** rat CLi 11.0 mL/min/g liver, human CLi 12.0 mL/min/g liver, CYP450 IC_{50} values all >4 μM (1A2, 2C19, 2C9, 2D6 and 3A4 isoforms); **9b** rat CLi 16.0 mL/min/g liver, human CLi 22.0 mL/min/g liver, CYP450 IC_{50} values ⩾11 μM at 1A2, 2C19, 2C9, 2D6 and 3A4 isoforms; **9f** rat CLi 26.0 mL/min/g liver, human CLi 19.0 mL/min/g liver; **9g** rat CLi 23.0 mL/min/g liver, human CLi 44.0 mL/min/g liver; **9k** rat CLi 32.0 mL/min/g liver, human CLi 26.0 mL/min/g liver.
21. After the preparation of this manuscript, a publication from Ono Pharmaceutical Co. Ltd appeared in the literature detailing the replacement of the carboxylic acid in compounds related to ONO-8713 (**4**) by functional groups such as acylsulfonamides and a phthalamide Naganawa, A.; Matsui, T.; Ima, M.; Saito, T.; Murota, M.; Aratani, Y.; Kijima, H.; Yamamoto, H.; Maruyama, T.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2006**, *14*, 7121.
22. In vitro metabolic stability data (intrinsic clearance, CLi) for compounds **10b**, **10c**, **10h** and **10l** in rat and human liver microsomes: **10b** rat CLi 17.0 mL/min/g liver, human CLi 9.1 mL/min/g liver; **10c** rat CLi 14.0 mL/min/g liver, human CLi 3.2 mL/min/g liver, CYP450 IC_{50} values 1–8 μM at 1A2, 2C19, 2C9 and 3A4 isoforms, IC_{50} value 22 μM at 2D6 isoform; **10h** rat CLi >50.0 mL/min/g liver, human CLi 15.0 mL/min/g liver, CYP450 IC_{50} values ⩾10 μM at 2D6 and 3A4 isoforms, IC_{50} 6.9 μM (1A2), 7.6 μM (2C19) and 2.2 μM (2C9); **10l** rat CLi 9.1 mL/min/g liver, human CLi 4.9 mL/min/g liver, CYP450 IC_{50} values ⩾10 μM at 2C19, 2C9, 2D6 and 3A4 isoforms, 1A2 isoform IC_{50} 3.6 μM.
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