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Synthesis of pyranoquinolines *via* imino Diels-Alder reaction: Comparison of antibacterial efficacy of chirally separated individual diastereomers

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The first ever attempt to separate the four diastereomers formed during pyranoquinoline synthesis *via* imino Diels-Alder reaction mediated by chiral catalyst is successful. The comparison of the antibacterial efficacy of individual diastereomers is revealed.

Keywords: Diels-Alder reaction, diastereomer, bactericidal activity, chiral catalyst, antibacterial activity

Chirality of drugs, particularly the comparison of efficacy of enantiomers and their racemic mixtures, has become an objective of serious interest of pharmaceutical researchers. Advances in chemical technologies connected with the synthesis, separation, and analysis of pure enantiomers from racemates, together with administrative regulatory measures, have resulted in an increase in the number of newly registered chiral drugs containing only one of the enantiomers.

Pyranoquinoline derivatives are an important class of natural products and exhibit a wide spectrum of biological activities, such as antiallergic, anti-inflammatory, anti pyretic, analgesic, antiplatelet, psychotropic and estrogenic. Hence, the synthesis[1] of pyranoquinoline derivatives is, currently, of much importance. Imino Diels-Alder reactions catalysed with triphenylphosphonium perchlorate[2a], Urea nitrate[2b], Iodine[2c], Bismuth[2d], Vanadium[2e], Indium[2f], Zirconium[2g], Lanthanum salts[2h-2j], Niobium[2k], Antimony[2l] were established. *Trans*-fused pyrano-and furano-tetrahydroquinolines[3] were synthesized under solvent-free conditions through phosphomolybdic acid-catalyzed aza Diels-Alder reactions. The pyrano- and furanoquinoline derivatives were prepared by aza Diels-Alder reactions of imines with different dienophiles, such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran, in the presence of different acid catalysts[3]. Ionic liquid mediated pyrano-and furanoquinolines synthesis was also attempted[4].

One-pot procedures for the aza Diels-Alder transformation by using lanthanide triflates as catalyst were attempted as well[5]. Recently much work has been devoted to the diastereoselective imino Diels-Alder reaction, but only few reports are available in the asymmetric imino Diels-Alder reactions[6-10]. Sundararajan *et al.*[11] have used (*R*,*R*)-3-aza-3-benzyl-1,5-dihydroxy-diphenylpentane ligated Ti(IV) complex (**1**-$TiCl_2$) as a chiral Lewis acid catalyst for promoting asymmetric imino Diels-Alder reaction between electron-rich dienophiles and electron-poor dienes. They concluded that **1**-$TiCl_2$ complex is quite effective for asymmetric the imino Diels-Alder reaction of benzylidine aniline and the reaction conditions were optimized to give moderate yields and enantioselectivities.

Chemistry

Studies on the diastereoselective imino Diels-Alder reaction mediated by chiral salen-$AlCl_3$ complex and synthesis of pyrazolyl tetrahydroquinolines catalysed by chiral shift reagents have been carried out by our research group[12]. From our previous study it was concluded that the bactericidal and bacteriolytic activities of one diastereomer was potentially active while the other was not only inactive but also brought about the competitive inhibition of the active diastereomer. The previous report was based on the manual column purification of the isomers. In the present work, we proceeded with the synthesis of pyranoquinolines, resolution of all the four diastereomers with chiral HPLC and evaluation of their antibacterial efficacy.

Results and Discussion

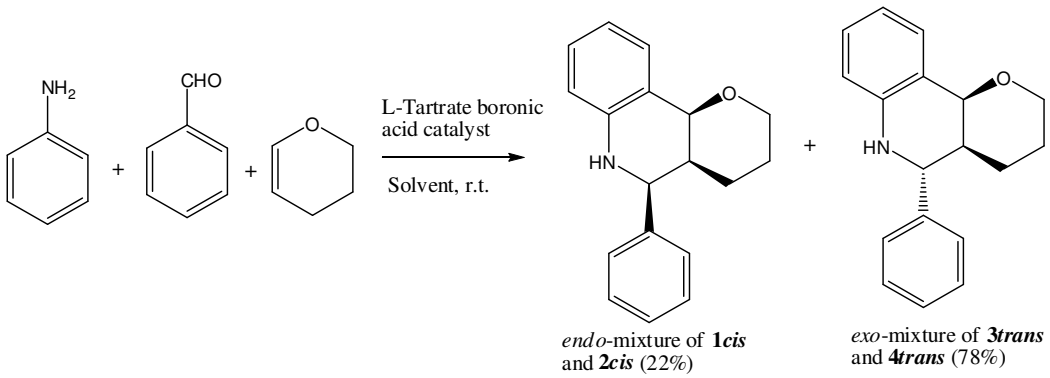
The present work describes the employment of the acyloxy boron catalyst for synthesis the pyranoquinolines by a one-pot two-component coupling of benzaldehyde aniline and 3,4-dihydropyran (**Scheme I**). The reaction was found to proceed smoothly to afford the corresponding pyrano-[3,2-*c*]quinoline as a mixture of *endo*-and *exo*-isomers (were distinguished by NMR[13]) in a ratio of 1:2, in an overall yield of 85%. These isomers were separated by column chromatography over silica gel. The purified diastereomers were found to be racemic even when the chiral ligand-Boron complex catalyst was employed. Both *endo*-and *exo*-diastereomeric mixtures were separated with CHIRALCEL-OD-H column to obtain four individual isomers (**Table I**). The similar corresponding furoquinolines diastereomers were synthesized (**Scheme II**) and purified.

According to our objective the separated four diastereomers were subjected to screening of bactericidal activity (**Table II**) following the similar protocol adopted by us earlier[12]. The activity of purified individual two *endo* pyranoquinoline diastereomers (**1** *cis* and **2** *cis*: mirror images of each other) and two *exo*-pyranoquinoline diastereomers (**3** *trans* and **4** *trans*: mirror images of each other) were compared with *endo*-mixture (**1** *cis* **+ 2** *cis*) and *exo*-mixture (**3** *trans* **+ 4** *trans*). Similarly, the activity of purified individual two *endo* furoquinoline diastereomers (**5** *cis* and **6** *cis*: mirror images of each other) and two *exo*-furoquinoline diastereomers (**7** *trans* and **8** *trans*: mirror images of each other) were compared with *endo*-mixture (**5** *cis* + **6** *cis*) and *exo*-mixture (**7** *trans* + **8** *trans*).

The individual *exo*-diastereomers at R_t 7.2 and 16.9 min along with pyranoquinoline *exo*-mixture (**3** *trans* **+ 4** *trans*) showed better antibacterial activity in overall. This complies with the fact that the *trans* or the *exo*-isomers whether as mixture or separated found to be active. It was also observed that *endo* individual isomers **1** *cis* and **2** *cis* or *endo* mixture showed less or no bactericidal activity and the individual diastereomer at R_t 16.9 min was found to be the most active among all the tested compounds indicating the importance of activity studies of the chirally separated diasteromers. This implies that the excess potency of this isomer is attributed not only to its *exo*-geometry alone, but also from its effective and stereospecific binding to the receptor sites on the bacteria. Also the bactericidal activity of the mixture of *exo*-isomers is majorly due to the isomer at R_t 16.9 min and not because of the less active isomer at R_t 7.2 min. And in the case of *V. harveyi*, isomer at R_t 7.2 min actually suppresses the overall activity of the *exo*-mixture.

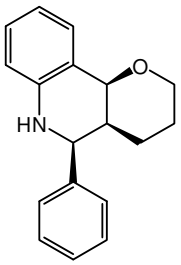
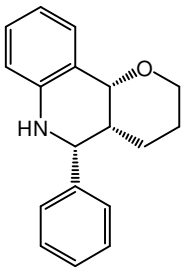
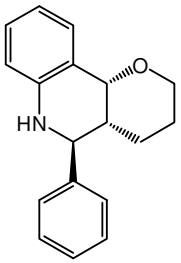
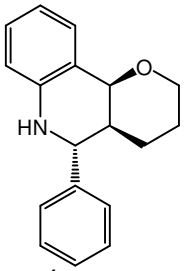
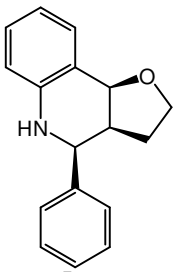
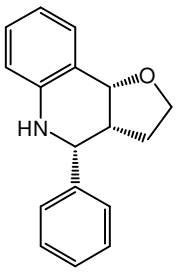
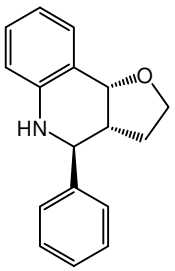
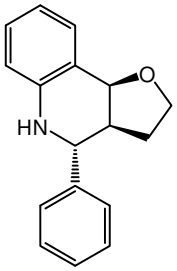
Similarly in the case of furanoquinolines only one *exo* isomer at R_t 8.7 min was found to be active, while all the other individually separated diastereomers or their mixture of *exo* or *endo* isomers found to be inactive showing the requirement and distinctiveness of a specific isomer for activity.

The bacteriolytic activity (**Table III**) of the isomers R_t 7.2 and 16.9 min was found to be good, while the other individual isomers or the *exo* or *endo* mixtures were inactive. This again is in agreement with *exo* requirement for the activity. It was also observed that individual *exo* isomer R_t 16.9 min was better in activity in comparison with the other *exo* isomer R_t 7.2 min. The obtained results were further established with the well diffusion assay (**Table IV**). Again the zone of inhibition observed for *exo* isomer R_t 16.9 min was better than isomer R_t 7.2 min whereas all the remaining isomers or mixtures were found to be inactive.



Scheme I — Synthesis of pyranoquinolines.

Table I — Synthesis of chirally pure pyranoquinoline and furanoquinoline adducts

S. No	Starting materials	Time (hr)	Yield[a] (%) *endo*: *exo*	Products (Diastereomeric pairs)[b,c]	R_t-**1** (min)	R_t-**2** (min)
1	$C_6H_5NH_2$ + C_6H_5CHO + 3,4-dihydro pyran	4	22:78	 **1*cis***  **2*cis***  **3*trans***  **4*trans***	8.4 7.2	13.6 16.9
2	$C_6H_5NH_2$ + C_6H_5CHO + 2,3-dihydro Furan	4	40:60	 **5*cis***  **6*cis***  **7*trans***  **8*trans***	9.8 7.6	15.9 19.9

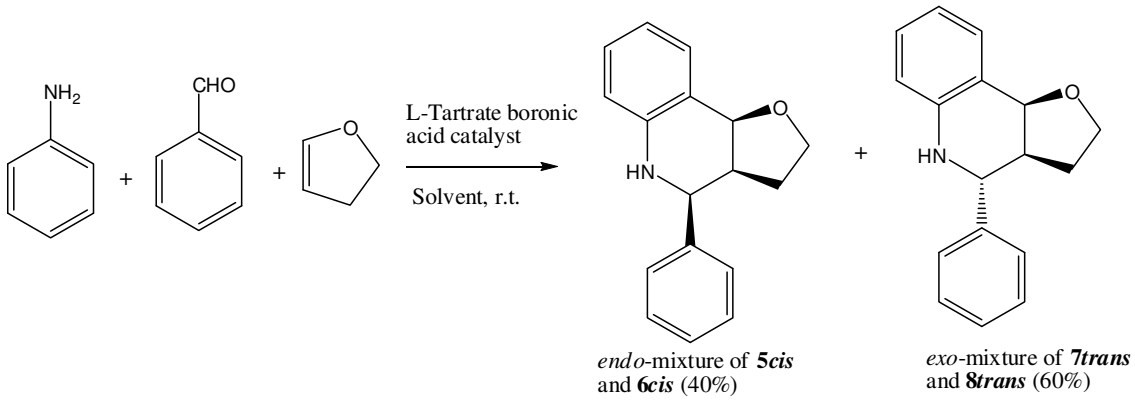
[a]Yield ratio of any two *endo* or *exo* isomer mixture is 50:50

[b]The mixture of *endo* products, **1** *cis* and **2** *cis* is racemic; and the mixture of *exo* products **3** *trans* and **4** *trans* is also racemic; Similarly, the mixture of *endo* products **5** *cis* and **6** *cis* and *exo* products **7** *trans* and **8** *trans* are racemic

[c]R_t mentioned in the parenthesis is the retention time of the individual isomers (unidentified) after chiral HPLC purification

General procedure for the preparation of pyranoquinolines

In a typical procedure, benzaldehyde (1.0 mmol) and aniline (1.0 mmol) was reacted with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (2.0 mmol, 2 equiv.,) in the presence of ligand, mono(2,6-dimethoxy-benzoyl)tartaric acid (0.4 mmol, 40 mol %) and a catalytic amount of borane in THF (0.2 mmol, 20 mol. %) in dry DCM (30 mL) at –78°C for 2 hr and then at RT for 6 hr. The reaction mixture was



Scheme II — Synthesis of furoquinolines.

Table II — *In vitro* bactericidal activity of chirally pure pyranoquinoline adducts

S. No	Bacterial pathogens	Bactericidal activity of compounds[a,b]						
		1 *cis*	**2** *cis*	**3** *trans*	**4** *trans*	**1** *cis* + **2** *cis*	**3** *trans* + **4** *trans*	Unresolved
1	*V. cholera*	+	+	+	+++	-	+	-
2	*V. parahemolyticus*	-	-	-	+	-	+	-
3	*V. vulnificus*	-	-	+	+	-	-	-
4	*V. aliginolyticus*	-	-	-	+++	-	+	-
5	*V. harveyi*	-	-	-	+++	-	++	+
6	*E. coli*	-	-	+	+++	-	-	+
7	*P. aeruginosa*	-	-	+	+++	+	++	+
8	*S. aureus*	+	+	+	+++	-	++	+

(+): Mild Bactericidal activity, (++): moderate Bactericidal activity, (+++): Strong Bactericidal activity, (-): Bactericidal activity was not observed. [b]Rest of the compounds exhibit no activity

then quenched with ice (30 mL) and satd. sodium bicarbonate solution (25 mL). The resultant product mixture was extracted with $CHCl_3$ (4 × 15 mL), washed with brine and dried over anhydrous Na_2SO_4, filtered and the solvent evaporated. The residue was purified by column chromatography (silica gel, 230-400 mesh; 10% EA/petroleum ether as eluent) with petroleum ether/ethyl acetate to afford the cycloadducts, namely the *endo* and *exo*-isomers in a ratio of 1:2, in an overall yield of 85%. The purified diastereomers were again chirally purified using CHIRALCEL OD-H column hexane:isopropanol (80:20) as mobile phase with 1.0 mL/min flow rate.

Procedure for *in vitro* bactericidal activity

The test compound (20 mg) was dissolved in 500 µL of DMSO. A volume of 5 µL (0.2 mg approx) of the stock solution was taken and 95 µL bacterial suspension in Tris buffer saline (0.8 OD at 580 nm) was added to it. The mixture was incubated at 14°C for 14 hr. After incubation was added with 10 µL of XTT (5mg/mL) dye for all 96 wells including control and incubated for 12-18 hr at 37°C. Yellow colour of the dye remains same, indicates strong bactericidal activity.

Procedure for *in vitro* antibacterial activity

Bacterial suspension in Tris buffer saline was prepared with an optical density of 0.8 OD at 580 nm (double beam UV spectrometer). TBS (Tris buffer saline) served as the blank. Add 150 µL of test compound (10 mg/mL) which was dissolved in DMSO and 2850 µL of bacterial suspension at the optical density of 0.8 OD at 580 nm. The initial OD of the sample was recorded. The mixture was incubated for 90 min at 23°C, mixture is recorded as final OD and compared with control OD. Initial OD – final OD gives the antibacterial activity.

Table III — *In vitro* antibacterial activity of chirally pure pyranoquinoline adducts

S. No	Bacterial pathogen[a]	Compd @ R_t – 7.2 min			Compd @ R_t – 16.9 min		
		Final OD	Act. OD	AB	Final OD	Act. OD	AB
1	*V. cholera*	0.786	0.045	+	0.746	0.085	++
2	*V. parahemolyticus*	0.79	0.041	+	0.739	0.092	+++
3	*V. vulnificus*	0.775	0.056	++	0.759	0.072	++
4	*V. alginolyticus*	0.7	0.049	+	0.734	0.097	+++
5	*V. harveyi*	0.78	0.055	++	0.752	0.079	++
6	*E. coli*	0.77	0.059	++	0.73	0.101	+++
7	*P. aeruginosa*	0.78	0.048	+	0.742	0.089	++
8	*S. aureus*	0.78	0.054	++	0.747	0.084	++

[a]Bacterial suspension in optical density (OD = 0.8) and initial OD = 0.831. (+): Mild antibacterial activity, (++): moderate antibacterial activity, (+++): Strong antibacterial activity, AB = antibacterial activity

Table IV — *In vitro* antibacterial activity of chirally pure pyranoquinoline adducts

S.No	Bacterial pathogens	Zone of Inhibition in mm[a,b]	
		Compd – RT 7.2 min	Compd – RT 16.9 min
1	*V. cholera*	20	26
2	*V. parahemolyticus*	20	21
3	*V. vulnificus*	12	20
4	*V. alginolyticus*	12	18
5	*V. harveyi*	26	32
6	*E. coli*	13	16
7	*P. aeruginosa*	15	22
8	*S. aureus*	16	20

[a]Antibacterial activity with well diffusion assay. [b]Rest of the compounds exhibit no remarkable activity.

Procedure for Well diffusion assay

Well diffusion assay (Fazeli *et al.,* 2007) is used widely to determine the antibacterial activity of compounds. The technique works well with defined inhibitions. Nutrients agar prepared was poured in the Petri dish. Bacterial cultures, 17 hr old *(V. cholera, V. parahemolyticus, V. vulnificus, V. alginolyticus, V. harveyi, E. coli, P. aeruginosa, S. aureus)* were spread separately over the surface of the dried agar plates using a sterile cotton swab and allowed to absorb in the agar for 10 min. Cut the well by using cork borer and load 2 mg/mL concentration of each compound in each well in middle well serves as a (DMSO) control. Incubated the plates at 37°C for 24 hr, and then measured the diameter of zone of inhibition.

All the compounds were characterized by FT-IR, NMR (400 MHz), MS, optical rotation, and chiral HPLC. The spectroscopic data were fully consistent with the assigned structures.

Selected spectroscopic data

Pyran adduct (*endo*-first, R_t @ 8.4 min): m.p. 132.6°C; FT-IR (neat): 3376, 2939, 1476, 1115, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54-7.41 (m, 5H), 7.36 (t, 1H, *J* = 7.2 Hz), 7.1 (dt, 1H, *J* = 1.88, 9.52 Hz), 6.89 (m, 1H), 6.72 (m, 1H), 5.33 (d, 1H, *J* = 5.48 Hz), 4.71 (d, 1H, *J* = 2.32 Hz), 3.63 (m, 1H), 3.47 (m, 1H), 2.22 (m, 1H), 1.65-1.30 (m, 4H); MS: *m/z* 266 ($M+H^+$); $[\alpha]^{23}$ = –64.6° (C = 0.104 g/mL; in $CHCl_3$); Chiral HPLC (CHIRALCEL OD-H SC\601): R_t = 8.4 min (mobile phase = 85% Hexane+15% IPA; Flow Rate: 1.0 mL/min)

Pyran adduct (*endo*-second, R_t @ 13.6 min): m.p. 130.9°C; FT-IR (neat): 3375, 2938, 1476, 1117, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47-7.38 (m, 5H), 7.35 (t, 1H, *J* = 7.10 Hz), 7.14 (t, 1H, *J* = 7.40 Hz), 6.87 (t, *J* = 7.44 Hz, 1H), 6.69 (d, *J* = 7.64 Hz, 1H), 5.34 (d, 1H, *J* = 5.44 Hz), 4.71 (d, 1H, *J* = 2.28 Hz), 3.62 (m, 1H), 3.47 (m, 1H), 2.22

(m, 1H), 1.60– 1.26 (m, 4H); MS: *m/z* 266 ($M+H^+$); $[\alpha]^{23}$ = +52.36° (C = 0.11 g/mL; in $CHCl_3$); Chiral HPLC (CHIRALCEL OD-H SC\601): R_t = 13.6 min (mobile phase = 85% Hexane+15% IPA; Flow Rate: 1.0 mL/min).

Pyran adduct (*exo*-first, R_t @ 7.2 min): m.p. 131.5°C; FT-IR (neat): 3366, 2936, 1486, 1083, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48-7.34 (m, 5H), 7.25 (m, 1H), 7.13 (dt, 1H, *J* = 1.40, 7.72 Hz), 6.81 (t, *J* = 7.44 Hz, 1H), 6.56 (d, *J* = 8.04 Hz, 1H), 4.76 (d, 1H, *J* = 10.88 Hz), 4.44 (d, 1H, *J* = 2.60 Hz), 4.26 (brs, 1H), 4.14 (m, 1H), 3.78 (m, 1H), 2.21 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 1.36 (m, 1H); MS: *m/z* 266 ($M+H^+$); $[\alpha]^{22.8}$ = +2.837° (C = 0.14 g/mL; in $CHCl_3$); Chiral HPLC (CHIRALCEL OD-H SC\601): R_t = 7.2 min (mobile phase = 85% Hexane+15% IPA; Flow Rate: 1.0 mL/min).

Pyran adduct (*exo*-second, R_t @ 16.9 min): m.p. 129.2°C; FT-IR (neat): 3367, 2937, 1486, 1083, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47-7.36 (m, 5H), 7.27 (m, 1H), 7.14 (dt, 1H, *J* = 1.52, 7.72 Hz), 6.82 (t, *J* = 7.36 Hz, 1H), 6.55 (d, *J* = 8.04 Hz, 1H), 4.76 (d, 1H, *J* = 10.88 Hz), 4.54 (brs, 1H), 4.44 (d, 1H, *J* = 2.64 Hz), 4.14 (m, 1H), 3.77 (m, 1H), 2.21 (m, 1H), 1.89 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 1.37 (m, 1H); MS: *m/z* 266 ($M+H^+$); $[\alpha]^{23.3}$ = –2.308° (C = 0.156 g/mL; in $CHCl_3$); Chiral HPLC (CHIRALCEL OD-H SC\601): R_t = 16.9 min (mobile phase = 85% Hexane+15% IPA; Flow Rate: 1.0 mL/min).

Furan adduct (*endo*-first, R_t @ 9.8 min): m.p. 107.0°C; FT-IR (neat): 3310, 2910, 1482, 1058, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 2H, *J* = 7.28 Hz), 7.42-7.37 (m, 4H), 7.13 (dt, 1H, *J* = 1.52, 8.08 Hz), 6.87 (t, 1H, *J* = 7.40 Hz), 6.65 (d, 1H, *J* = 8.00 Hz), 5.31 (d, 1H, *J* = 7.96 Hz), 4.72 (d, 1H, *J* = 3.00 Hz), 3.87 (m, 1H), 3.77 (m, 1H), 2.83 (m, 1H), 2.29 (m, 1H), 1.57 (m, 1H); MS: *m/z* 252 ($M+H^+$); $[\alpha]^{23.1}$ = –42.105° (C = 0.114 g/mL; in $CHCl_3$); Chiral HPLC (CHIRALCEL OD-H SC\601): R_t = 9.8 min (mobile phase = 85% Hexane+15% IPA; Flow Rate: 1.0 mL/min).

Furan adduct (*endo*-second, R_t @ 15.9 min): m.p. 106.0°C; FT-IR (neat): 3309, 2912, 1483, 1058, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 2H, *J* = 7.28 Hz), 7.42-7.37 (m, 4H), 7.13 (dt, 1H, *J* = 1.48, 8.44 Hz), 6.88 (t, 1H, *J* = 7.32 Hz), 6.67 (d, 1H, *J* = 8.00 Hz), 5.30 (d, 1H, *J* = 7.96 Hz), 4.72 (d, 1H, *J* = 2.96 Hz), 3.87 (m, 1H), 3.77 (m, 1H), 2.84 (m, 1H), 2.27 (m, 1H), 1.60 (m, 1H); MS: *m/z* 252 ($M+H^+$); $[\alpha]^{22.8}$ = +36.99° (C = 0.11 g/mL; in $CHCl_3$); Chiral HPLC (CHIRALCEL OD-H SC\601): R_t = 15.9 min (mobile phase = 85% Hexane+15% IPA; Flow Rate: 1.0 mL/min).

Furan adduct (*exo*-first, R_t @ 7.6 min): m.p. 107.0°C; FT-IR (neat): 3321, 2929, 1484, 1040, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (m, 6H), 7.16 (t, 1H, *J* = 7.96 Hz), 6.90 (t, 1H, *J* = 7.44 Hz), 6.70 (d, 1H, *J* = 7.96 Hz), 4.66 (d, 1H, *J* = 5.12 Hz), 4.07 (m, 1H), 3.88 (m, 2H), 2.58 (brs, 1H), 2.09 (m, 1H), 1.74 (m, 1H); MS: *m/z* 252 ($M+H^+$); $[\alpha]^{24}$ = –39.818° (C = 0.11 g/mL; in $CHCl_3$); Chiral HPLC (CHIRALCEL OD-H SC\601): R_t = 7.6 min (mobile phase = 85% Hexane+15% IPA; Flow Rate: 1.0 mL/min).

Furan adduct (*exo*-second, R_t @ 19.9 min): m.p. 108.0°C; FT-IR (neat): 3321, 2927, 1485, 1040, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 6H), 7.17 (dt, 1H, *J* = 1.48, 7.72 Hz), 6.96 (t, 1H, *J* = 7.36 Hz), 6.73 (d, 1H, *J* = 7.96 Hz), 4.69 (d, 1H, *J* = 5.24 Hz), 4.07 (m, 1H), 3.89 (m, 2H), 2.70 (brs, 1H), 2.10 (m, 1H), 1.73 (m, 1H); MS: *m/z* 252 ($M+H^+$); $[\alpha]^{22.8}$ = +32.816° (C = 0.103 g/mL; in $CHCl_3$); Chiral HPLC (CHIRALCEL OD-H SC\601): R_t = 19.9 min (mobile phase = 85% Hexane+15% IPA; Flow Rate: 1.0 mL/min).

Conclusion

The argument is strengthened herein that stereo-specificity is essential criteria towards receptor binding, particularly with respect to antibacterial activity of pyrano-quinolines. And we were successful in this first ever attempt to compare the antibacterial activity of chirally pure individual pyrano-and furo-quinoline diastereomers. This preliminary result will facilitate our interests on tetrahydroquinolines as antibacterials.

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