A DIC Mediated Expeditious Small Library Synthesis and Biological Activity of Thiazolidin-4-one and 1,3-Thiazinan-4-one Derivatives

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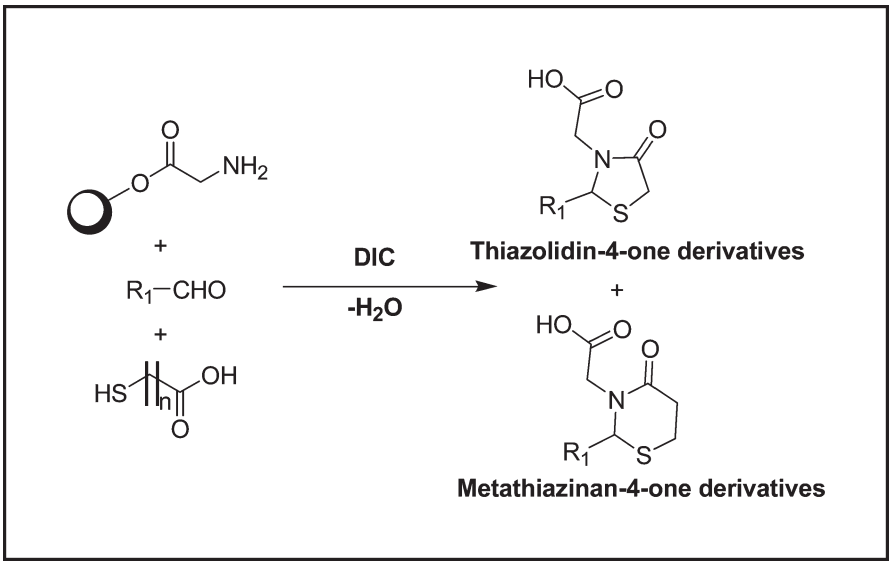

A diisopropylcarbodiimide (DIC) mediated small library of thiazolidin-4-one and 1,3-Thiazinan-4-one derivatives were efficiently synthesized using one pot three component condensation of amino acid, aldehyde, and mercapto carboxylic acid on a polymer support. The study shows significantly higher yields of the thiazolidin-4-one derivatives thereby indicating a lower dependence on the nature of the amino acid and aldehyde components. As an obvious extension of this protocol, the reactions were performed using heterocyclic aldehydes and substituted hindered aromatic aldehydes instead of simple aromatic aldehydes. The synthesized library compounds were also screened for their antifungal acitivity against these three pathogenic fungi: *Candida albicans (Ca), Candida parapsilosis (Cp)*, and *Cryptococcus neoformans (Cn)*.

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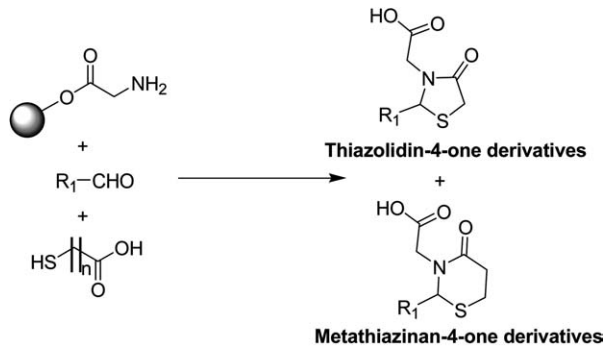
INTRODUCTION

The categorical imperative of modern drug discovery is to produce better clinical candidates that are less prone to failure at later stage. Solid phase organic synthesis is regarded as one of the key disciplines for providing constant supply of chemical compounds that may be monitored for their biological activity on the vastly increasing number of biological targets. Solid phase organic synthesis together with high throughput synthesis and efficient data management, undoubtedly lead to acceleration in the process of drug discovery [1].

There are numerous biologically active molecules whose framework includes a five-membered and six-membered ring containing two hetero atoms. Thiazolidin-4-one and thiazinan-4-one are biologically important scaffolds known to be associated with several biological activities. These structures contain one **S** and one **N** atom in skeleton as heterocyclic atoms [2–3].

Several protocols for the synthesis of thiazolidin-4-one and thiazinan-4-one derivatives are available in the literature [4–12] (Scheme 1). Essentially these are three component reactions involving an amine, a carbonyl compound and a mercapto acid. The process can be either a one-pot three-component condensation or a two-step process. The reaction has been suggested to proceed via imine formation followed by the attack of sulfur nucleophile on the imine carbon. The last step involves intramolecular cyclization with the elimination of water to give the final compound. This step appears to be

Scheme 1. Schematic representation for synthesis of thiazolidin-4-one and metathiazinan-4-one derivatives on solid support.



critical for obtaining high yields. Therefore, variations have been affected in this step to facilitate removal of water. Most commonly used protocols utilize azeotropic distillation, molecular sieves, and use of other desiccants like anhydrous zinc chloride [13], sodium sulfate [14], or magnesium sulfate [15]. These protocols require prolonged heating at 70–80°C for 17–20 h and give moderate to good yields. More recently, an improved protocol has been reported wherein *N*,*N*-dicyclohexylcarbodiimide (DCC) or 2-(1H-benzotrizole-1-yl)-1,1,3,3 tetramethyluraniumhexafluorophospate (HBTU) is used as an acid amine coupling and dehydrating agent to accelerate intramolecular cyclization, resulting in faster reaction and improved yields [16,17]. First time Holmes *et al*. [18] reported solution and polymer-supported synthesis of thiazolidin-4-one and thiazinan-4-one derivatives, derived from amino acids. In amino acids, the carboxylic acid function serves as an anchor group for attachment to the site of support. The condensation of this support bound amine with several aldehydes and mercapto acetic acids in a one-pot reaction, afforded desired products. A series of experiments were performed using different proportions to optimize the ratio of reactants. The ratio of reactants in 1:2:3 for amino acid, aldehyde, and mercapto acetic acid, respectively, as in case of solution phase HBTU protocol gave poor yields. Quantitative yields were obtained by using the ratio of reactants in 1:4:6 for amino acid, aldehyde, and mercapto acetic acid, respectively. This is in agreement with the earlier observation by Holmes *et al*. In a typical experiment, amino acid and aldehyde were shaken in dry tetrahydrofuran (THF) for 15 min, followed by addition of mercapto acetic acid and HBTU, and shaking of reaction mixture for an additional 5 h. The resin was then filtered, washed successively with *N*,*N*′-dimethyl formamide (DMF) (3 × 2 mL), methanol (MeOH) (3 × 2 mL), dichloromethane (DCM) (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum. After cleavage of the final compounds from the resin by treating it with trifluroacetic acid (TFA): dichloromethane (DCM) (1:1) mixture, the desired products in almost quantitative yields were obtained. It was observed that in the case of phenylalanine, the yields were significantly lower than that with glycine, using HBTU in both the reactions. Fast decomposition of HBTU and steric hindrance could be a major reason for lower yield with phenylalanine.

Previous studies suggest that the use of carboxylate activating reagents have facilitated cyclization [19]. Therefore it was thought to explore *N, N*′-diisoproplylcarbodiimide (DIC) as a coupling and dehydrating agent by keeping *N*,*N*- dicyclohexylcarbodiimide (DCC) mediated protocol in mind, which is usually used in solid phase peptide coupling reactions [20–21]. The generality of the DIC mediated reactions have been demonstrated by synthesizing a variety of thiazolidin-4-one and thiazinan-4-one derivatives. In previous study, it was observed that sterically hindered amino acids react sluggishly during cyclization and lead to poor yields or sometimes do not react at all. To avert these shortcomings, in this study, sterically hindered amino acids were examined and the results obtained were excellent (Table-2).

Candida albicans, Candida parapsilosis, and *Cryptococcus neoformans* are the common opportunistic fungi responsible for infections. Out of these *Candida albicans* infections may become problematic in severely immunocompromised patients and may induce oral candiasis,

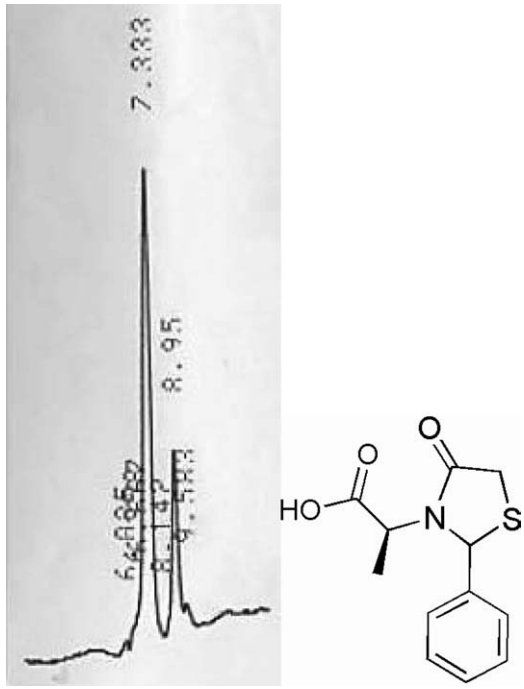
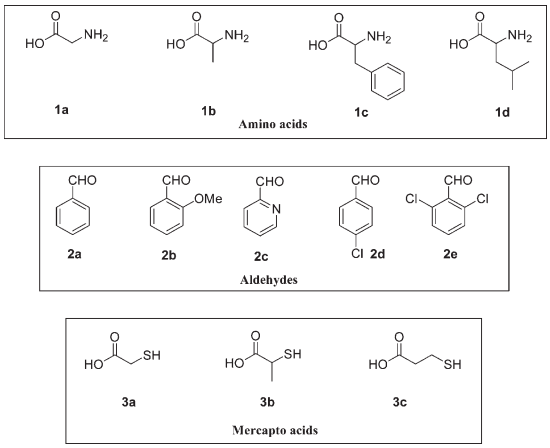


Figure 1. The HPLC data of the final compound VI. HPLC trace of diastereomeric thiazolidin-4-one (VI) (7.333 and 8.95 min) after TFA cleavage from solid support at 220 nm.

oesophageal candiasis, and vaginal candiasis. *Candida parapsilosis* is second to *Candida albicans* as a cause of candida endocarditis. Approximately 25% of candidal endocarditis cases reported have been caused by *Candida parapsilosis*. On the contrary *Cryptococcus neoformans* is the causative agent of cryptococcosis, which is the leading cause of morbidity and mortality due to fungi in patients with AIDS. Thus, there is urgent need for more effective and novel antifungal therapies. Therefore in the first instance, synthesized library compounds were screened for their antifungal activity, against these three pathogenic fungi: *Candida albicans (Ca), Candida parapsilosis (Cp)*, and *Cryptococcus neoformans (Cn)*.

Table 1

Building blocks for solid phase synthesis.



EXPERIMENTAL

The reagents used in the study are figured in Table 1. Unless otherwise stated, the materials were of the highest grade available from commercial sources and used without further purification. The solvents and reagents were purchased from the following sources: Wang resin (1% divinylbenzene, 200–400 mesh, 0.5–1.2 mmol/g substitutions) from Novabiochem; Fmoc protected amino acids, *N*,*N*′-diisopropylcarbodiimide, piperidine, diisopropylamine, and trifluoroacetic acid from Aldrich and mercapto acid derivatives from Lancaster.

The reactions on solid phase were optimized using polypropylene syringes of 5 mL capacity (Becton and Dickinson) with fritt (12 mm diameter and 2 mm thickness for 5 mL syringes) inserted at the bottom of the syringes. They were shaken on an orbital shaker (IKA-Vibrax-VXR). The syringes were capped at the bottom with Leur positive (VSG-0419, Roland Vetter) cap. The compounds after cleavage from the resin were dried under N_2. ^{1}H NMR spectra were obtained on Brucker Evans DRX-600 spectrometer and chemical shifts (δ) were reported in ppm relative to TMS. Because of solubility properties, the solvents used was $CDCl_3$. RP-HPLC analysis of crude products was carried using a 5 μm, 4.8 × 150 mm C-18 reverse-phase column with a linear gradient of Acetonitrile:Water (80:20 v/v) with 100 μL TFA over 25 min. The flow rate was 0.4 mL/min, and UV detection was observed at 220 nm. The retention time of compounds has been expressed in minutes as t_R (Fig. 1). Mass spectra were recorded using electron spray ionization (ESI) technique or FAB.

Ninhydrine test for aliphatic primary amines. Ninhydrine test is used to detect the presence and absence of free aliphatic $-NH_2$ group on resin beads after de-protection of Fmoc group. The test was performed by taking small aliquot of the resin in an eppendorf followed by the addition of few drops of following solutions:

1. 80% solution of phenol in absolute alcohol.
2. 2% solution of aqueous KCN (0.001*M*) in Pyridine.
3. 5% solution of Ninhydrine in absolute alcohol.

The eppendorf was then heated at 100°C in a water bath, for 5 min. and colour of the beads was examined. The presence of free aliphatic $-NH_2$ group of amino acids was indicated by blue resin beads (Positive Ninhydrine test), whereas its absence was confirmed by colorless beads (Negative Ninhydrine test).

GENERAL PROCEDURE

Loading of amino acid on resin. The Wang resin (500 mg) was swelled by shaking on an orbital shaker (IKA-Vibrax-VXR) at 600 rpm in 5 mL DCM:DMF (1:1) for 30 min. The resin was then filtered and washed with DMF. The resin so obtained was then coupled with a preactivated solution of amino acid (5 equiv., 2.825 mmol), DIC (3 equiv., 1.695 mmol, 267.38 μL) and DMAP (3 equiv., 1.695 mmol, 207 mg) in dry DMF (2 mL) and the reaction mixture was allowed to shake at room temperature for 6–7 h. The resin was filtered and washed, successively, with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum. A second repeat cycle was made with a preactivated solution of amino acid (2 equiv., 1.13 mmol), DIC (1.5 equiv., 0.847 mmol, 133.5 μL) and DMAP (1.5 equiv., 0.847 mmol, 103.5 mg) in dry DMF (2 mL), and the reaction mixture was allowed to shake at room temperature for 6–7 h to achieve complete loading of amino acids on resin. The resin was filtered and washed, successively, with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum. (Scheme 2).

Deprotection of Fmoc groups of resin bound amino acids. This was carried out by treating the resin twice with 30% (v/v) piperidine/DMF solution at room temperature for 15 and 25 min, respectively. Then the resin was filtered and washed successively with DMF (3 × 2

mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum.

Preparation of resin bound thiazolidin-4-one and thiazinan-4-one derivatives. The Fmoc-deprotected amino acids loaded Wang resin (200 mg in a polypropylene syringe) was swelled in dry THF for 30 min. After 30 min (hetero)/aromatic aldehyde (4 eq.) in THF was added and shook on an orbital shaker (IKA-Vibrax-VXR) at 600 rpm for 30 min. Then, an appropriate mercapto acid (6 eq.) was poured into the reaction mixture. After 5 min diisopropylcarbodiimide (DIC) (4 eq.) was added to the reaction mixture. The reaction mixture was then allowed to shake at room temperature for 8 h. Diisopropylurea (DIU) was separated during reaction was removed by washing. The resin was then filtered, washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and diethylether (3 × 2 mL) and dried in vacuum.

Cleavage of final compounds (I–XXIII). The final compounds (Table 2) were cleaved from the resin by treating it with TFA:DCM (1:1) mixture. The resulting mixture was filtered and the filtrate was evaporated to dryness in vacuum.

ANTIFUNGAL ACTIVITY

The IC_{50} values of library compounds were determined against the test fungi by using micro-broth dilution technique as per guidelines of NCCLS M-27A [22]. IC_{50} values of standard antifungal (Miconazole) and synthetic compounds were measured in 96 well tissue culture plate (CellStar Greiner Bio One, Germany) using RPMI 1640 media buffered with MOPS [3-(*N*-Morpholino) propanesulfonic acid, Sigma]. Starting inocula of test culture were maintained at 1.0–5.0 × 103 cfu/mL. A solution of 2 mg/mL of library compounds in 10% DMSO was used. Microtitre plates were incubated at 35°C in a moist dark chamber and IC_{50} and MIC values were recorded spectrophotometrically (Softmax pro 4.3, Versamax microplate reader, molecular devices) after 48 h for *candida albicans* and *candida parapsilosis* and 72 h for *cryptococcus neoformans*. The antifungal

Scheme 2. DIC mediated synthesis of thiazolidin-4-one and metathiazinan-4-one derivatives. Reagents and conditions: (i) 5 mL DCM:DMF (1:1), 30 min (ii) 10 equiv. FmocAA-OH (1a–d), 5 equiv. DMAP, 5 equiv. DIC, dry DMF, rt, 600 rpm, 6h. (iii) 20% piperidine in dry DMF, rt, two cycles of 15 and 30 min, respectively. (iv) 4 equiv. aldehyde(2a–e), 6 equiv. mercapto acid (3a–c), 4 equiv. DIC, rt, 8 h. (v) 20% TFA/DCM, rt, 1h.

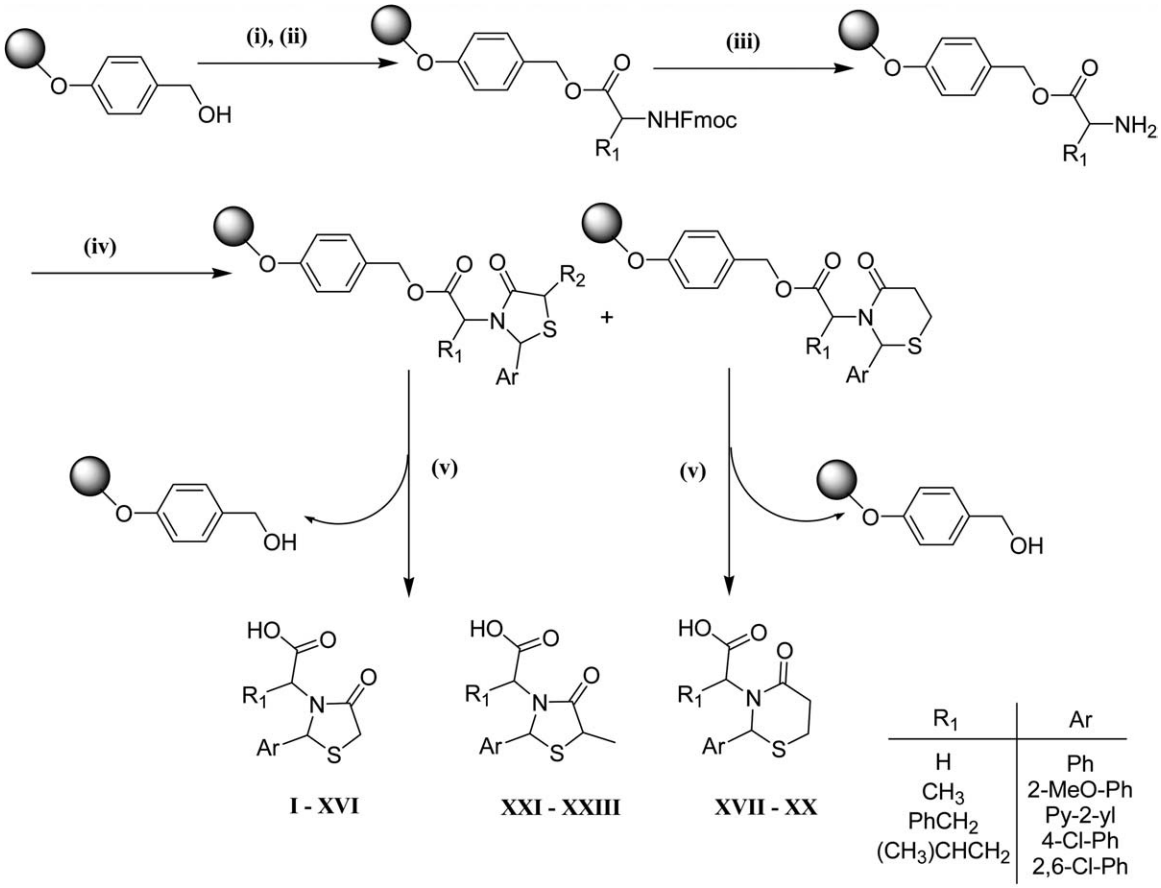


Table 2

Data of compounds synthesized on solid phase.

Entry	Building blocks			Overall yields[a] (%)	M.Wt	ESI-MS *m/z* $(M+H)^+$
	Amino acids	Aldehydes	Mercapto acids			
I	1a	2a	3a	98	237	238
II	1a	2b	3a	90	267	268
III	1a	2c	3a	96	238	239
IV	1a	2d	3a	66	271	272
V	1a	2e	3a	95	306	307
VI	1b	2a	3a	90	251	252
VII	1b	2b	3a	63	281	282
VIII	1b	2c	3a	55	252	253
IX	1b	2d	3a	30	285	286
X	1c	2a	3a	75	327	328
XI	1c	2b	3a	42	357	358
XII	1c	2c	3a	53	328	329
XIII	1c	2d	3a	28	361	362
XIV	1c	2e	3a	58	396	397
XV	1d	2a	3a	89	293	294
XVI	1d	2b	3a	42	323	324
XVII	1a	2c	3c	68	252	253
XVIII	1b	2a	3c	40	265	266
XIX	1c	2a	3c	80	341	342
XX	1c	2b	3c	32	371	372
XXI	1b	2c	3b	62	266	267
XXII	1c	2b	3b	36	371	372
XXIII	1d	2a	3b	40	307	308

[a] The overall yields are based on the initial loading of hydroxymethyl resin.

activity of library compounds has been summarized in Table 3.

RESULTS AND DISCUSSION

Physicochemical data. ***(4-Oxo-2-pyridin-2-yl-thiazolidin-3-yl)-acetic acid (III).*** mp semisolid on RT: IR (KBr) 1681.81, 1745.46; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.56 (bs, 1H, OH), 3.44 (d, J = 18.0 Hz, 1H, NCH_2), 3.76 (d, J = 15.6 Hz, 1H, H_A), 3.82 (dd, J = 15.6, 1.2 Hz, 1H, H_B), 4.39 (d, J = 18.0 Hz, 1H, NCH_2), 6.01 (s, 1H, C-2), 7.40 (m, 1H, H_5-Py), 7.58 (d, J = 7.8 Hz, 1H, H_3-Py), 7.88 (m, 1H, H_4-Py), 8.53 (d, J = 4.8 Hz, 1H, H_6-Py); ^{13}C NMR (CDCl3) δ 32.18, 45.00, 63.13, 122.88, 124.72, 139.23, 147.82, 157.82, 169.73, 172.11.

2-(4-Oxo-2-phenyl-thiazolidin-3-yl)-propionic acid (VI). mp 176–182°C (3:1 mixture of diastereomers): IR (KBr) 1664.45, 1685.67, 1743.53; ^{1}H NMR ($CDCl_3$, 600 MHz) δ major isomer 1.25 (d, J = 7.8 Hz, 3H, CH_3), 3.67 (d, J = 16.2 Hz, 1H, H_A), 3.85 (dd, J = 16.2, 1.2 Hz, 1H, H_B), 4.21 (q, J = 7.2 Hz, 1H, C*H*CH_3), 5.20 (bs, 1H, OH), 5.75 (s, 1H, C-2), 7.35–7.45 (m, 5H, Ph); minor isomer, 1.41 (d, J = 7.8 Hz, 3H, CH_3), 3.73 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.77 (s, 2H, CH2), 5.20 (bs, 1H, OH), 5.74 (s, 1H, C-2), 7.35–7.45 (m, 5H, Ph); 13C NMR (CDCl3) δ major isomer 14.24, 32.41, 52.60, 63.24, 127.11, 128.23, 129.11, 137.78, 172.35, 172.96; minor isomer 14.38, 33.10, 53.46, 65.69, 127.11, 128.23, 129.82, 139.74, 172.35, 172.96.

2-(4-Oxo-2-phenyl-thiazolidin-3-yl)-3-phenyl-propionic acid (X). mp 75–81°C (3:1 mixture of diastereomers): IR (KBr) 1681.81, 1745.46; ^{1}H NMR ($CDCl_3$, 600 MHz) δ major isomer 3.23–3.27 (m, 1H, CH_2-Ph), 3.31–3.48 (m, 1H, CH_2-Ph), 3.66–3.76 (m, 2H, H_A & H_B), 3.89 (q, J = 6.0, 0.5H, CH), 5.07 (q, J = 6.0, 0.5H, CH), 6.74 (bs, 1H, OH), 6.87 (s, 0.5H, C-2), 6.98 (s, 0.5H, C-2), 7.14–7.41 (m, 7H, Ar-H), 7.48 (t, J = 7.2, 1H, H5-benzyl), 7.68 (d, J = 7.20, 2H, $H_{2\&6}$-Ph); ^{13}C NMR (CDCl3) δ major isomer (32.66, 33.00), (33.10, 34.30), (58.97, 59.25), (65.49, 65.94), (126.65, 127.12), (128.48, 128.53), (128.62, 128.69), (128.84, 129.05), (129.24, 129.45), (129.72, 132.00), (133.48, 135.77), (136.44) 137.39), (172.22, 172.49), (173.67, 174.02).

The above findings draw attention to address the scope and limitations of the present protocol. The work concentrated on aldehydes having electron-donating and electron-withdrawing substituents. It is evident from the yields that the present method obviates the limitations of earlier methods and is more versatile. Furthermore, this method shows significantly higher yields of the thiazolidin-4-one derivatives thereby indicating a lower dependence on the nature of the amino acid and aldehyde components (Table 2). As an obvious extension of this

Table 3

IC_{50} values for synthesized library compounds (I–XXIII).

Entry	*Ca* IC_{50} [μ*M*]	*Cp* IC_{50} [μ*M*]	*Cn* IC_{50} [μ*M*]
I	82.37	82.37	53.45
II	79.49	79.49	79.49
III	78.61	78.61	78.61
IV	77.51	77.51	77.51
V	83.33	75.33	52.91
VI	78.12	78.12	43.28
VII	79.61	79.61	21.17
VIII	27.14	20.22	22.50
IX	79.61	79.61	33.91
X	78.49	52.90	24.01
XI	79.55	79.55	48.05
XII	80.64	80.64	15.16
XIII	78.67	56.17	49.80
XIV	22.01	13.54	12.16
XV	81.30	57.23	28.94
XVI	80.38	56.51	35.85
XVII	80.51	80.51	30.27
XVIII	75.24	52.89	23.70
XIX	55.36	56.28	47.09
XX	78.12	78.12	43.28
XXI	81.27	98.25	43.16
XXII	84.14	81.27	82.64
XXIII	78.16	79.52	78.32
Standard (miconazole)	05.12	08.22	01.32
Control	85.23	98.48	92.54

protocol, the reactions were performed using heterocyclic aldehydes and substituted hindered aromatic aldehydes instead of simple aromatic aldehydes. The corresponding thiazolidin-4-one derivatives were obtained in quantitative yield. Generally, low yields of thiazolidin-4-one derivatives were reported in the literature when amino acids were used as a source of amine; however, with this protocol, excellent to moderate yields were obtained. The versatility of the protocol and to further enhance the scope of this reaction, efforts were made on adaptation of the method for synthesis of thiazinan-4-one, another biologically active chromophore. It is apparent from the variety of reactants that this method has the potential to generate a battery of thiazolidin-4-one and thiazinan-4-one derivatives by solid phase combinatorial synthesis.

The results for the antifungal assay of the synthesized library compounds are summarized in Table 3. As is evident that out of 23 synthesized molecules, compound XIV exhibited best inhibitions in comparison to others with IC_{50} values of 22.01 μ*M* against *Ca*, 13.54 μ*M* against *Cp*, and 12.16 μ*M* against *Cn*.

Our studies thus suggest that activity is strongly dependent on the nature of the substituent at C-2 and N-3 positions of thiazolidin-4-one ring. In particular, a high activity level was observed for compounds possessing a 2,6-dihalophenyl group at C-2 position and a phenethyl ring at N-3 position.

The results presented in this study indicate that changes at C-2 position of thiazolidin-4-one moiety, except for 2,6-dihalophenyl, may lead to reduction in antifungal activity of these compounds. However, introduction of phenethyl moiety at the N-3 position in the thiazolidin-4-one ring is well-supported.

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