Computational and pharmacological investigation of novel 1,5-diaryl-1,4-pentadien-3-one derivatives for analgesic, anti-inflammatory and anticancer potential

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ABSTRACT

Objective(s): The novel 1,5-diaryl-1,4-pentadien-3-one derivatives were studied for analgesic, anti-inflammatory and antitumor potential to establish their role in pain, inflammatory disorders and cancer.

Materials and Methods: Two 1,5-diaryl-1,4-pentadien-3-one derivatives: (1E,4E)- 5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-methylpenta-1,4-dien-3-one (A2K2A17) and (1E,4E)-5-(4-nitrophenyl)-1-(4-nitrophenyl)-2-ethylhexa-1,4-dien-3-one (A11K3A11) were synthesized and characterized via 1H NMR and 13C NMR techniques. Molecular docking, anti-inflammatory, analgesic and anticancer activities were performed using Auto Dock Vina, carrageenan mediated paw edema and formalin induced chronic inflammation, acetate acid induced writhings and brine-shrimp lethality assay.

Results: A2K2A17 and A11K3A11 showed high computational affinities (binding energy > -9.0 Kcal/mol) against COX-1, kappa receptor and braf kinase domain. A2K2A17 and A11K3A11 exhibited moderate docking affinities (binding energy > -8.0 Kcal/mol) against COX-2, human capsacin receptor, tumor necrosis factor, lipoxygenase, colony stimulating factor, delta receptor, cyclin dependent protein kinase-2, mitogen activated kinase, mu receptor and kit kinase domain. A2K2A17 and A11K3A11 possess low docking affinities (binding energy > -7.0 Kcal/mol) against purinoreceptor, platelets-derived growth Factor-1 and vascular-endothelial growth factor. In analgesic activity, A2K2A17 (1-30 mg/kg) and A11K3A11 (1-10 mg/kg) decreased acetic acid induced writhings and prolonged the latency time (P<0.01, P<0.001 vs saline group) respectively. A2K2A17 (10-30 mg/kg) and A11K3A11 (1-10 mg/kg) reduced carrageenan as well as formalin mediated edema (P<0.01, P<0.001). A2K2A17 found effective for cytotoxicity assay with LC50 value 1.5 µg/ml.

Conclusion: The in silico, in vitro and in vivo studies on A2K2A17 and A11K3A11 reports their computational binding affinities against targets as well as the analgesic, anti-inflammatory and the anticancer-effects.

Introduction

Pain is an unpleasant sensation which is associated with tissue damage (1). Noxious effects such as ulceration, gastrointestinal bleeding by nonsteroidal anti-inflammatory drugs and drowsiness, nausea and tolerance by opioid analgesics limit their use in pain management (2).

Inflammation is the reaction of living tissues to injury. It includes different events such as activation of enzyme, release of inflammatory mediator and fluid extravasation, migration of cell, tissue breakdown and repair (3, 4). Inflammatory ailments remains one of the major health concerns (5, 6). The adverse effects with nonsteroidal anti-inflammatory drugs (NSAID’s) such as gastric lesions, dependence and tolerance produced by opioids, use of NSAID’s and opiates has not been effective in all cases (7, 8).

Cancer is diverse group of progressive disorders, characterized by the abnormal and rapid proliferation and is a major problem worldwide. To cope with this problem new site selective drug discovery and development is required (9).

The 1,5-diarylpentanoid dibenzylidene acetone is the parent structure having an acyclic di-enone attached with aryl groups at b-position. These structures are similar to those of the curcuminoid (1, 7-diaryl heptanes) and the chalcone (1, 3-diaryl propanes). The synthetic chalcone have shown different pharmacological activities; antitumor (10), antioxidant (11) and anti-inflammatory (12, 13).Two 1,5-diaryl-1,4-pentadien-3-one derivatives are: (1E,4E)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-methylpenta-1,4-dien-3-one (A2K2A17) and (1E,4E)-5-(4-nitro phenyl)-1-(4-nitrophenyl)-2-ethylhexa-1,4-dien-3-one (A11K3A11) were synthesized. A2K2A17 and A11K3A11 were studied for analgesic, anti-inflammatory and anticancer effects, using different computational and pharmacological assays. The structures of A2K2A17 and A11K3A11 are shown in Figure 1.

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Materials and Methods

Chemicals

Acetic acid (DAEJUNG Reagents Chemicals), carrageenan (Sigma-Chemicals Co, St-Louis, USA), dimethyl sulphoxide (DMSO), diclofenac (Olive Labs National industrial zone, Islamabad, Pakistan), Formalin (BDH Laboratory supplies, Poole, England), tramadol (Searle company limited F-319, Karachi, Pakistan), methotrexate and ethanol.

Test animals

Mice 25-30 g (Balb-C, n=5 in each group) were kept according to standard protocols (25 ± 2°C), with natural duration of Light/Dark cycle, each of 12 hrs. Healthy diet was given to mice and water ad libitum. The whole study was performed according to the protocols of Animal Resources Institute, Life Science University, National Research Council (NRC 1996), with prior approval by Ethics Committee of RIPS (Riphah Institute of Pharmaceutical Sciences) with Reference no; REC/RIPS-2016/0012.

Synthesis

The reaction of p-methoxy benzaldehyde with 2-butanone in the presence of HCl gas in dichloromethane produces intermediate compounds. The intermediate is further reacted with p-Flouro benzaldehyde in ethanol yielding compound A2K2A17. The synthesis of A2K2A17 is reported (14). A11K3A11 is synthesized by first reacting p-nitro benzaldehyde with 2-pentanone producing intermediate A11K3, which on further reaction with p-nitrobenzaldehyde produces compound A11K3A11 as shown in Scheme 1. Chemical characterization of A11K3A11 was carried out based on the analysis of spectroscopic and crystallographic data.

Computational analysis

Docking is a tool for computational analysis, which is used to investigate affinity and interaction between target protein and ligand (15). We used Auto Dock Vina program for docking study through PyRx. Affinity was determined using interactions of ligand with receptor complex and expressed in the form of binding-energy (E value, Kcal/mol). The 3D-structures of A2K2A17 and A11K3A11 were prepared through Bioviadiscovery Studio Visualizer (DSV) and saved as PDB format. The 3D-structures of target proteins were taken from http://www.rcsb.org/pdb../home.do. The proteins target involved in pain, inflammation and cancer pathways are cyclo-oxygenase-1 (COX-1, PDB-ID: 3N8X), cyclo-oxygenase-2 (COX-2, PDB-ID: IPXX), mu receptor (PDB-ID: 5CIM), kappa receptor (PDB-ID: 4DJH), delta receptor (PDB-ID: 4EJ4), human capsacin receptor (HCR, PDB-ID: 3J9I) and purinoceptor-3 (P2X3, PDB-ID: 5SVL), C-4 synthetase (PDB-ID: 2UH), tumor necrosis factor (TNF, PDB-ID: 1TNF), lipoxygenase (5-LOX, PDB-ID: 3OBY), colony stimulating factor (CSF, PDB-ID: 3UF2), cyclin dependent protein kinase-2 (CDPK-2, PDB-ID: 1HCL), mitogen activated kinase (MAK-ERK-1, PDB-ID: 2ZQQ), insulin like growth factor-1 (ILGF-1, PDB-ID: 1B9G), platelets derived growth factor-1 (PDGF-1, PDB-ID: 1PDG), braf kinase domain (PDB-ID, 4RSY), vascular...
endothelial growth factor (VEGF, PDB-ID: 1VPF), nuclear factor kappa (NFkB, PDB-ID: 1NFK) and kit kinase domain (PDB-ID: 3GOE). All target proteins were purified by Biovia Discovery Studio Client 2016. The 3D-structures of standard drug molecules were downloaded from the data base (https://pubchem.ncbi.nlm.nih.gov/search/). Standard analgesic, anti-inflammatory and anti-cancer drugs are aspirin (Pubchem-CID: 2244), apsazepine (Pubchem-CID: 2733484), morphine (Pubchem-CID: 5288826), thymoquinone (Pubchem-CID: 10281), vemurafenib (PubChem-CID: 42611257), sunitinib (PubChem-CID: 5329102), curcumin (PubChem-CID: 969516) and itraconazole (PubChem-CID: 5793). All these structures were taken in form of XML and converted to PDB-Format using Open-Babel JUI software. PDB form of both ligand and standard as well as target proteins are converted to PDBQT via Auto Dock Tools (Version1.5.6 Sep_17_14). Both test compounds along with protein targets were loaded in software named as PyRx and then docked against respective targets binding affinity was calculated shown in Kcal/mol. For post docking interaction Discovery studio visualizer was used for number of hydrogen bond (classical/non-classical) and binding residues of amino-acid: Alanine (ALA), Asparagine (ASN), Arginine (ARG), Cysteine (CYS), Aspartic acid (ASP), Glutamine (GLN), Serine (SER), Proline (PRO), Glutamic acid (GLU), Glycine (GLY), Histidine (HIS), Tryptophan (TRP), Threonine (THR), Tyrosine (TYR), Valine (VAL), Leucine (LEU), Lysine (LYS) and Phenylalanine (phe).

**Analytic activity**

**Acetic acid induced writhings**

The analgesic potential of test compounds was determined by acetic acid induced writhings in mice (16). The animals after 12 hr fasting were divided into 5 different groups (5 mice in each group). After 30 min of the administration of A2K2A17 (1, 10, 20 and 30 mg/kg, IP) and A11K3A11 (1, 5 and 10 mg/kg), writhings were induced by intraperitoneal injection (IP) of acetic acid (0.1 ml, 0.7% v/v) to induce pain. Pain perception was recorded in the form of stretch of hind limb and abdominal constriction called as writhes. Some mice showed half writhes. Two half writhes were considered as equal to one full writhes. The writhings were recorded for 20 min. Normal saline (10 ml/kg) was given to saline treated group-negative control while diclofenac (20 mg/kg) was administered to positive control group.

**Hot plate assay**

The mice were distributed into 5 different groups (n=5 in each group). The mice were placed on hot plate individually (55±2 °C) and observations (licking paws or jumping) at 30, 60, 90 and 120 min were measured. The latency period of test compounds: A2K2A17 (1, 10, 20 and 30 mg/kg) and A11K3A11 (1, 5 and 10 mg/kg), were evaluated via hot plate assay according to the protocols with little modifications (17). Normal saline (10 ml/kg) was given to control group, tramadol 30 mg/kg (centrally acting opioid analgesic) was used as positive control.

**Anti-inflammatory models**

**Carrageenan mediated paw edema**

The mice were fasted overnight. The displacement of paw was determined using Plethysmometer, Ugo-Basei, before administering any drug (18). The animals were placed into 5 groups (5 mice in each group). Acute inflammation was induced in mice by carrageenan subplantar injection (0.1 ml, 1% w/v). Saline (10 ml/kg) was given to negative control group. Half an hr prior to carrageenan injection, the animals were administered with test compound: A2K2A17 (10, 20 and 30 mg/kg) and A11K3A11 (1, 5 and 10 mg/kg) IP. The standard drug diclofenac sodium (20 mg/kg), was administered to the positive control group. The paw volume was measured at 0 to 5 hr, with 1 hr interval following carrageenan injection (19).

**Formalin induced edema**

The anti-inflammatory potential against chronic inflammation was determined using formaldehyde mediated edema (20). The animals were divided into 5 groups (n=5). The base line paw volume displacement was determined using Plethysmometer. Inflammation induced by sub-aponeurotic administration of formalin (0.1 ml, 2% v/v formaldehyde) in the left hind paw on first day and third day. Normal saline (10 ml/kg)
Spectral analysis of A11K3A11

| Target       | PDB ID(s) | mol/m | mol/m | H-Bonds | mol/m | H-Bonds | mol/m | H-Bonds | mol/m | H-Bonds | mol/m | H-Bonds |
|--------------|-----------|-------|-------|---------|-------|---------|-------|---------|-------|---------|-------|---------|
| COX-1        | 3SNK      | 9.1   | 2     | 9.8     | 7     | -6.6    | 3     | 48       | 20.77 | 13.65   | 125.85 |
| COX-2        | 1PIX      | -8.5  | 3     | -9.9    | 4     | Aspirin | -7.0  | 3        | 27.0  | 7.0     | 8.4   | 1       |
| Mu opioid    | 5C1M      | -8.3  | 2     | -7.9    | 1     | Morphine| -7.2  | 0        | 124.38| 124.03  | 20.77 | 13.65   |
| Kappa opioid | 4DPH      | -9.1  | 2     | -9.7    | 0     | Morphine| -8.0  | 0        | 124.38| 124.03  | 20.77 | 13.65   |
| Delta opioid | 1EJ4      | -8.4  | 0     | -8.4    | 1     | Morphine| -7.2  | 0        | 124.38| 124.03  | 20.77 | 13.65   |
| HCR          | 59J       | -8.5  | 1     | -8.7    | 1     | Capsaicin| -8.2  | 3        | 120.7 | 75      | 5.4   | 8.2     |
| P2X3         | 55VL      | -7.2  | 1     | -7.7    | 2     | GLY-40  | -5.4  | 2        | 120.7 | 75      | 5.4   | 8.2     |

Table 1. E-value (Kcal/mol) and post-docking analysis of best pose of (1E,4E)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-methylpent-1,4-dien-3-one(A2K2A17), (1E,4E)-5-(4-nitrophenyl)-1-(4-nitrophenyl)-2-ethylhexa-1,4-dien-3-one(A11K3A11) and standard drugs with cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), mu receptor, kappa receptor, delta receptor, human capsaicin receptor (HCR) and purinoreceptors P2X3.

Table 2. The latency time of saline (10 ml/kg) treated group showed 90.20 ± 1.068 numbers of writhes. The writhes count of A2K2A17 (1, 10, 20 and 30 mg/kg) treated groups decreased to 74.40 ± 1.32, 47.40 ± 1.43, 41.00 ± 1.14 and 32.20 ± 1.77 (P<0.001 vs saline group) (Figure 2A). The writhes count of A11K3A11 (1, 5 and 10 mg/kg) decreased to 28.80 ± 1.77 (P<0.001 vs. saline group) (Figure 2A). The writhes count of A2K2A17 and A11K3A11 with target proteins: braf kinase domain, CDPK-2, MAK-ERK-1, ILGF-1, PGDF-1, VEGF, NFKB and kit kinase domain involved in cancer pathway along with standard drugs are shown in Table 3.

Effect on latency time in hot plate assay

The latency time of saline (10 ml/kg) treated group at 0, 30, 60, 90, 120 min was 7.35 ± 0.12, 8.33 ± 0.13, 8.56 ± 0.10, 8.71 ± 0.10 and 8.70 ± 0.03 sec respectively. A2K2A17 dose dependently (1, 10, 20 and 30 mg/kg) prolonged latency time (P<0.01 vs. saline group) against thermal pain generation (Figure 3A). A11K3A11 dose dependently (1, 5 and 10 mg/kg) prolonged latency time (P<0.01 vs. saline group) against thermal pain generation (Figure 3A).
Table 2. E-value (Kcal/mol) and post-docking analysis of best pose of (1E,4E)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-methylpenta-1,4-dien-3-one (A2K2A17), (1E,4E)-5-(4-nitrophenyl)-1-(4-nitrophenyl)-2-ethylhexa-1,4-dien-3-one (A11K3A11) and standard drugs with C4-synthetase, tumor necrosis factor (TNF), lipooxygenase (5-LOX) and colony stimulating factor (CSF)

| Target          | PDB-ID | E-value (Kcal/mol) | Binding residues | Binding residues | Standard | Keal/mo | No of H-Bonds | Binding residues | Keal/mo | No of H-Bonds | Binding residues |
|-----------------|--------|--------------------|------------------|------------------|----------|---------|--------------|------------------|---------|--------------|------------------|
| C4-synthetase   | 2UIH   | -10.0              | 0                | NIL              | NIL      | -10.0   | 0            | -10.0            | 0       | 0            | -10.0            |
| TNF             | 1TNF   | -8.1               | 0                | GLU-104          | GLU-104 | -8.0    | 0            | -8.0             | 0       | 0            | -8.0             |
| 5-LOX           | 308Y   | -0.0               | 0                | ASN-328          | ASN-328 | -0.4    | 0            | -0.4             | 0       | 0            | -0.4             |
| CSF             | 319P   | -8.7               | 0                | LYS-100          | LYS-100 | -8.7    | 1            | -8.7             | 1       | 0            | -8.7             |

Figure 3. A and B represents the effect of (1E,4E)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-methylpenta-1,4-dien-3-one (A2K2A17) and (1E,4E)-5-(4-nitrophenyl)-1-(4-nitrophenyl)-2-ethylhexa-1,4-dien-3-one (A11K3A11) respectively on latency time in hotplate assay. Data expressed as mean ± SEM, n=5. **P<0.01, ***P<0.001 vs. saline group, one way analysis of variance with post hoc Tukey’s test.

Figure 4. A and B represents the effect of (1E,4E)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-methylpenta-1,4-dien-3-one (A2K2A17) and (1E,4E)-5-(4-nitrophenyl)-1-(4-nitrophenyl)-2-ethylhexa-1,4-dien-3-one (A11K3A11) respectively on carrageenan induced paw edema in mice. Values shown are mean±SEM, n=5. **P<0.01, ***P<0.001 vs. saline group, one way analysis of variance with post hoc Tukey’s test.
Table 3. E-value (Kcal/mol) and post-docking analysis of best pose of (1E,4E)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-methylpent-1,4-dien-3-one(A2K2A17), (1E,4E)-5-(4-nitrophenyl)-1-(4-nitrophenyl)-2-ethylhexa-1,4-dien-3-one (A11K3A11) and standard drugs with braf kinase domain, cyclin dependent protein kinase-2 (CDPK-2), mitogen activated kinase (MAK-ERK-1), insulin like growth factor-1 (ILGF-1), platelet derived growth factor-1 (PDGF-1), vascular endothelial growth factor (VEGF), nuclear factor kappa b (NFkB) and kit kinase domain

| Target                      | PDB-ID's   | E-value Kcal/mol | No of H-Bonds | Binding residues | E-value Kcal/mol | No of H-Bonds | Binding residues | Standard     | Kcal/mol     | No of H-Bonds | Binding residues |
|-----------------------------|------------|------------------|----------------|------------------|------------------|----------------|------------------|--------------|--------------|----------------|-----------------|
| Braf kinase domain          | 4KSY       | -0.1             | 1              | ASP             | 594              | -9.3           | 3                | THR-529, SER-436, VAL | 5.35         | 3            | 5.06           | GLN, SER-436, VAL |
| CDPK-2                      | 1HCL       | -0.3             | 2              | LYS             | 129              | GLY-131        | -7.8             | 1            | LYS          | 33             | Sunitinib      |
| MAK-ERK-1                   | 22DQ       | -0.6             | 3              | ARG             | 187              | 165            | 189              | -8.4         | ARG          | 187, 165, 189  | Sunitinib      |
| ILGF-1                      | 1BP6       | -5.8             | 1              | THR             | 4                | -6.0           | 2                | LYS          | 55           | THR-4         | Sunitinib      |
| PDGF-1                      | 1PGD       | -6.3             | 2              | VAL              | 39               | SER-50         | -7.1             | 2            | ARG          | 55             | Sunitinib      |
| VEGF                        | 1PVF       | -7.0             | 3              | CYL             | 59                | GLY-48         | -7.8             | 1            | LYS          | 48             | Sunitinib      |
| NFkB                        | 1NPK       | -6.6             | 3              | SER              | 72               | SER-136        | -6.0             | 3            | SER          | 110, LYS-146  | Sunitinib      |
| Kit kinase domain           | 3GO       | -8.0             | 2              | THR              | 670              | ASP-810        | -8.5             | 3            | ARG          | 815            | Sunitinib      |

Glutamine (GLN), cysteine (CYS), arginine (ARG), tyrosine (TYR), serine (SER), glutamic acid (GLU), threonine (THR), histidine (HIS), asparagine (ASN), valine (VAL), lysine (LYS), isoleucine (ILE), glycine (GLY) and aspartic acid (ASP)

time (P<0.01 vs. saline group) against thermal pain generation (Figure 3B). Tramadol (30 mg/kg) reduced the latency (P<0.001 vs. saline group).

Effect of A2K2A17 and A11K3A11 on Carrageenan mediated paw edema

A2K2A17 (10-30 mg/kg) reduced the carrageenan mediated inflammation in a dose dependent way (Figure 4A). The subplantar injection of carrageenan produce edema which progressively increases in the saline treated control group. Treatment of animal with A2K2A17 (10-30 mg/kg) and A11K3A11 (1-10 mg/kg) decreased carrageenan mediated paw inflammation (P<0.05, P<0.01, P<0.001 vs saline group) as presented in Figure 4 (A and B) respectively. Similarly, diclofenac (20 mg/kg) decreased the carrageenan induced inflammation in paw.

Effect on formalin mediated inflammation

A significant increase in the left hind paw thickness was observed in the saline treated control group after formalin injection. Continuous treatment with A2K2A17 (10-30 mg/kg) and A11K3A11 (1-10 mg/kg) remarkably reduces paw edema (P<0.05, P<0.01, P<0.001 vs saline). The reduction in paw thickness was observed from the day 1st and throughout the time period of study (10 days), compared with saline treated group shown in Figure 5 (A and B) respectively. Diclofenac at dose of 20 mg/kg reduces the paw edema (P<0.001 vs saline group).

Effect on brine shrimp lethality

A2K2A17, A11K3A11 and methotrexate exhibited concentration-dependent (1, 3, 5, 10, 100, 300 and 1000 µg/ml) cytotoxic effect against brine shrimps (Table 4). The larvae killed by A2K2A17 and A11K3A11, with LC₅₀ value of 1.50 µg/ml and 107.29 µg/ml respectively. The cytotoxic effect by methotrexate occurs at LC₅₀ value of 3.39 µg/ml.

Figure 5. A and B represents the effect of (1E,4E)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-methylpent-1,4-dien-3-one (A2K2A17) and (1E,4E)-5-(4-nitrophenyl)-1-(4-nitrophenyl)-2-ethylhexa-1,4-dien-3-one (A11K3A11) respectively on formalin induced inflammation in hind paw of mice. Values shown are mean±SEM, n=5. *P<0.05, **P<0.01, ***P<0.001 vs. saline group, one way analysis of variance with post hoc Tukey's test
Discussion

Molecular docking has gained valuable importance in the field of drug development. The main purpose of docking is to get the preliminary information about affinity of any compound before the start of in vivo experiment. The docking of novel 1, 5-diaryl-1, 4-pentadien-3-one derivative i.e, A2K2A17 and A11K3A11 were carried out using Autodock Vina program through PyRx (22). Docking tool was preliminary tool used to check the affinity of ligands to their respective protein targets. These interactions may be in the form of hydrogen bonds, hydrophobic interaction and Van der Waal forces (23). Hydrogen bonding has significant role in the formation of ligand protein complex. In this study we assessed affinity of ligand using three parameters: E-value, number of hydrogen bond and amino acid residue against the protein targets involve in pain, inflammation and cancer. A2K2A17 order of affinity against target protein was found as: COX-1 > kappa receptor > braf kinase domain > COX-2 > HCR > CSF > kit kinase domain > TNF > MAK-ERK-1 > lipoxygenase > delta receptor > mu receptor > CDPK > VEGF > P2X3 > PDGF-1 > NFK > C-4 synthetase > ILGF-1. A11K3A11 order of affinity against target proteins was found as: COX-1 > kappa receptor > kit kinase domain > MAK-ERK-1 > COX-2 > HCR > delta > mu receptor > CDPK > braf kinase domain > TNF > lipoxygenase > CSF > P2X3 > C4 synthetase > VEGF > NFK > PDGF-1’ > ILGF-1.

The analgesic activity was tested with two protocols; Acetic acid induce writhes method and hot plate assay, to evaluate the peripheral as well as central effects of analgesia (24). A2K2A17 and A11K3A11 showed dose-dependent analgesic effect. A2K2A17 is more effective in increasing the latency period compared to A11K3A11, while both compounds were equally effective against formalin mediated paw edema. The test compounds were effective in reduction of the formalin induced cellular damage. The test compounds were investigated for in vitro cytotoxicity using brine shrimps assay. The lethality of brine shrimp is because of less developed membrane susceptibility to cytotoxic chemical (15). A2K2A17 was found to be more effective with 1.5 µg/ml LC50 value as compared to A11K3A11, with 107.29 µg/ml LC50 value. Moreover the anticancer potential needs further investigation by screening the test compounds through cell line assays using human cancer cells.

Conclusion

Computational studies reveal binding affinities of 1,5-diaryl-1,4-pentadien-3-one derivatives: A2K2A17 and A11K3A11 against proteins targets involved in the pathogenesis of pain, inflammation and cancer as well as exhibit analgesic, anti-inflammatory and anticancer activities which explore their therapeutic effectiveness in pain, inflammatory disorders and tumor. Further studies are warranted to determine safety profile, pharmacokinetics and pharmacodynamics of test compounds to establish them as lead molecules.

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Conflicts of Interest

The authors declare no conflicts of interest.

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